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Diagnostic and Therapeutic Challenges in Neurological Diseases: A Beginner's Guide to *primum non nocere*

Habilitationsschrift

zur Erlangung der venia legendi im Fach Neurologie an der
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Für meinen Vater

Abstract

One of the central ethical precepts in medicine is to do no harm. Balancing safety, risks and benefits of healthcare decisions is an everyday challenge in routine clinical practice. Depending on the medical problem at hand, refraining from an intervention may be better or safer than risking harm. Further, diagnostic inaccuracy may lead to a misdiagnosis, which may also lead to harm.

With this work, I am highlighting the knowledge gained through my research of diagnostic and therapeutic challenges in neurological diseases such as multiple sclerosis, chronic inflammatory demyelinating polyneuropathy, Moyamoya angiopathy and aseptic meningitis. Findings derived from our real-world population-based studies filled major knowledge gaps as drugs used to treat multiple sclerosis are usually only tested in highly regulated trials over 2-3 years before market approval. Multiple sclerosis drug treatment exposure (versus no exposure) was associated with differences in infection-related healthcare use. Infection-related hospitalizations and physician visits were lower whereas prescription fills were higher. Further, with an observational study, we were able to scrutinize the relevance of misdiagnoses and delay in the diagnoses of patients with Moyamoya angiopathy. In chronic inflammatory demyelinating polyneuropathy patients (versus healthy controls), optical coherence tomography examination revealed subtle evidence for retinal degeneration while multifocal visual evoked potential measurements did not differ between the groups. In aseptic meningitis, findings of our observational study suggest that enterovirus-positive cases usually present with a more benign disease course and a shorter hospitalization period, compared to enterovirus-negative cases.

Taken together, state-of-the-art, non-invasive diagnostic tools (e.g. optical coherence tomography and multifocal visual evoked potentials) and population-based as well as observational studies examining the safety and benefits of diagnostic/therapeutic interventions may be considered (cost-)effective approaches to reduce the risk of harm for patients with a neurological disorder.

Zusammenfassung

Eines der zentralen ethischen Gebote in der Medizin lautet, keinen Schaden anzurichten. Das Abwägen von Sicherheit, Risiken und Nutzen von Entscheidungen ist eine alltägliche Herausforderung in der klinischen Routinepraxis. Je nach medizinischem Problem kann es besser oder sicherer sein, von einem Eingriff abzusehen, als einen Schaden zu riskieren.

Mit dieser Arbeit möchte ich die durch meine Forschung gewonnenen Erkenntnisse über diagnostische und therapeutische Herausforderungen bei neurologischen Erkrankungen wie Multipler Sklerose, chronisch entzündlicher demyelinisierender Polyneuropathie, Moyamoya-Angiopathie und aseptischer Meningitis hervorheben. Die Ergebnisse unserer bevölkerungsbasierten Studien schließen relevante Wissenslücken, da Medikamente zur Behandlung der Multiplen Sklerose in der Regel nur in streng regulierten Studien über einen Zeitraum von 2-3 Jahren vor der Marktzulassung getestet werden. Die Behandlung mit Multiple-Sklerose-Medikamenten (im Vergleich zu keiner Behandlung) war mit Unterschieden in der infektionsbedingten Inanspruchnahme der Gesundheitsversorgung verbunden. Infektionsbedingte Krankenhausaufenthalte und ambulante Arztbesuche waren seltener, wohingegen die Zahl der Arzneimittelverordnungen höher war.

Außerdem konnten wir in einer Beobachtungsstudie die Bedeutung von Fehldiagnosen und Verzögerungen bei der Diagnose von Patient:innen mit Moyamoya-Angiopathie untersuchen. Bei Patient:innen mit chronisch entzündlicher demyelinisierender Polyneuropathie (im Vergleich zu gesunden Kontrollpersonen) ergaben sich bei der optischen Kohärenztomographie subtile Hinweise auf eine Netzhautdegeneration, während die Messungen des multifokalen visuell evozierten Potenzials keine Unterschiede zwischen den beiden Gruppen zeigten. Bei der aseptischen Meningitis deuten die Ergebnisse unserer Beobachtungsstudie darauf hin, dass Enterovirus-positive Fälle im Vergleich zu Enterovirus-negativen Fällen in der Regel einen harmloseren Krankheitsverlauf und eine kürzere Krankenhausverweildauer aufweisen.

Zusammengefasst können moderne, nicht-invasive Diagnoseinstrumente (z. B. optische Kohärenztomographie und multifokale visuell evozierte Potenziale) und bevölkerungsbezogene sowie Beobachtungsstudien, die die Sicherheit und den Nutzen diagnostischer/therapeutischer Maßnahmen untersuchen, als (kosten-)wirksame Ansätze zur Verringerung des Schadensrisikos für Patienten mit einer neurologischen Erkrankung angesehen werden.

Abbreviations

ADR	Adverse drug reaction
aHR	Adjusted hazard ratio
aRR	Adjusted rate ratio
BC	British Columbia
CIDP	Chronic inflammatory demyelinating polyneuropathy
COVID-19	Corona virus diseases 19
cPIRA	Confirmed progression independent of relapse activity
CSF	Cerebrospinal fluid
DFG	German Research Foundation
DMD	Disease-modifying drug
EDSS	Expanded disability status scale
EMA	European Medicines Agency
FDA	Food and Drug Administration
ICD	International Classification of Diseases
IVIg	Intravenous immunoglobulin
JCV	John Cunningham virus
mfVEP	Multifocal visual evoked potentials
MMA	Moyamoya angiopathy
MS	Multiple sclerosis
NMOSD	Neuromyelitis optica spectrum disorder
OCT	Optical coherence tomography
STA-MCA	Bypass surgery between the superficial temporal artery and the middle cerebral artery
VZV	Varicella zoster virus

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1. Introduction

Primum non nocere – sometimes referred to as *nihil nocere* – is a central precept in medical ethics, which highlights the need for health care professionals to *'first, do no harm'*.[1] The origin of this Latin phrase remains uncertain[2], however, this maxim reminds healthcare staff to carefully consider potential harm of medical interventions. In short, balancing safety, risks and benefits of healthcare decisions is an everyday challenge in routine clinical practice, and – depending on the medical problem – to refrain from an intervention may be better or safer than risking harm. Therefore, recognizing risks and safety challenges is key in medical practice in order to prevent the two major types of medical errors[3]: First, "errors of omission occur as a result of actions not taken"[3] and second, "errors of the omission occur as a result of the wrong action taken"[3]. These errors remain a major cause of death just prior to the pandemic e.g. within the United States, underscoring their relevance in public health.[3] On the one hand, treatment- and intervention-related errors, harms and/or adverse events may be considered obvious and long-known healthcare challenges.[3,4] On the other hand, the consequences – and burden – of misdiagnoses and diagnostic-related harm/error, especially in diseases with treatment options, on the other hand should not be overlooked.[5,6] This holds especially true during outbreaks of infectious diseases e.g. COVID-19 or aseptic meningitis, when the healthcare system needs to function under particular pressure.

James Lind's "Treatise of the Scurvy" from 1753 is considered the beginning of evidence-based medicine. However, evidence-based medical interventions in neurological diseases – and therefore also their related harms, errors and adverse events – may also be considered a novelty. This is particularly the case in certain areas

of contemporary neurology, where therapeutic and also diagnostic advancements in multiple sclerosis (MS), chronic inflammatory demyelinating polyneuropathy (CIDP) and Moyamoya angiopathy (MMA) during the past decades may be considered ground-breaking.

MS is an immune-mediated disease of the central nervous system[7] which is often diagnosed in early adulthood. After trauma, MS is the second most common cause of sustained physical disability in young adults around the globe.[8] In MS, early treatment is key.[9] Thanks to advancements in refining the MS diagnostic criteria[10], diagnosing MS early has become increasingly realistic.

This is important as the economic impact of MS in Europe is remarkable: For example, in The Netherlands, the annual total direct (non-)medical and indirect costs per patient per year (2011) may be up to 100,000 EUR.[11] Despite the advances in MS treatment, there is no known cure so far. Today, persons with MS can have several disease-modifying drug (DMD) treatments to choose from. Especially the development of different monoclonal antibodies to treat MS (and other immune-mediated diseases) e.g. by targeting B cells[12] is worth mentioning because they are particularly beneficial.[13-15] In Germany, access to these drugs is facilitated by a rather generous reimbursement scheme, as compared to most other countries.[16] This provides patients access to all licensed DMDs without having to worry about high out-of-pocket drug expenses.

The DMDs used to treat MS typically gain regulatory approval after short-term (lasting 2-3 years), highly regulated clinical trials, conducted in select, carefully screened patients. In contrast, in routine clinical practice, a much broader range of MS patients may be expected to take these efficacious, but expensive, DMDs for many years. The effects of the different DMDs, along with the patient's age, sex, and comorbidities, on the MS disease course, and on the risk of harm such as an adverse drug reaction (ADR; 'side effect') remain poorly understood. This is despite the known healthcare burden associated with ADRs, which are a prominent issue within the healthcare system.[17] For example, ADRs are a relevant challenge in German healthcare[18]: In general, ADRs may be responsible for approximately 1 in 30 hospitalizations in Germany every year (2006-07). The average direct medical treatment cost of a single ADR is nearly 2,250 EUR. Twenty percent of ADR cases are thought to be preventable. If ADRs could be prevented or better managed, this would result in potential savings for the German healthcare system equal to 87 million EUR per year.[18]

Prominent examples of MS DMDs associated with ADRs are natalizumab and daclizumab[13]: Natalizumab treatment increases the risk progressive multifocal leukoencephalopathy (PML), a severe and often fatal viral infection mediated by the John Cunningham virus (JCV).[19] Due to this PML risk, natalizumab was withdrawn from the market from the US Food and Drug Administration (FDA) in 2005. However, after carefully reviewing safety, risks and benefits, natalizumab was reintroduced in 2006 under a special prescription program. Daclizumab was granted marketing authorization in 2016 by the FDA and European Medicines Agency (EMA) to treat MS, but was later found to increase the risk for a rare but fatal liver toxicity. This prompted the drug manufacturer to withdraw it from that market in 2018.[20] Hence, it is worthwhile

mentioning that post-marketing safety mechanisms have proven to function immediately after a series of relevant ADRs.

There are a plethora of safety mechanisms such as pharmacovigilance measures using e.g. 'spontaneous' reporting systems.[21,22] The vast majority of observational (MS) studies, however, focus on DMD effectiveness alone.[23,24] In addition to observational studies, both large cohort studies[25-28] and mobile health interventions[29] will become more and more relevant for healthcare planning, patient safety, identifying risk factors and treatment decisions in the future in order to provide the optimal quality of patient care[30]. With this habilitation treatise, I highlight the scientific insights in understanding patient safety we have gained within the past decade. Chapters 2 and 3 thoroughly summarize and discuss the results of my research.

2. Diagnostic Challenges in Neurological Diseases

2.1 Multiple Sclerosis

This chapter is based on the following Original Research articles:

Graf J, Akmatov MK, Meuth SG, Tremlett H, Holstiege J. Updated Multiple Sclerosis Incidence, 2015-2022. JAMA Neurol. 2024;81(10):1100-1102.

doi:10.1001/jamaneurol.2024.2876

Graf J, Leussink VI, Dehmel T, Ringelstein M, Goebels N, Adams O, MacKenzie CR, Warnke C, Feldt T, Lammerskitten A, Klotz L, Meuth S, Wiendl H, Hartung H-P, Aktas O, Albrecht P. Infectious risk stratification in multiple sclerosis patients receiving immunotherapy. Ann Clin Transl Neurol. 2017;4(12):909-914.

doi:10.1002/acn3.491

As already mentioned above, diagnosing MS early is key. The most recent, 2017 MS diagnostic criteria[31] aimed to both facilitate diagnosing MS and further shorten the latency between symptom onset and diagnosis for patients. Another objective was also to balance and mitigate the risk of a 'false positive' diagnosis. Briefly, a physician needs to prove both a dissemination in time and space in order to establish a diagnosis of MS in a patient. The 2017 criteria re-introduced oligoclonal bands in the cerebrospinal fluid (CSF) as an additional marker of dissemination in time, while cortical lesions can demonstrate dissemination in space. Further, the 2017 criteria permit both symptomatic and asymptomatic lesions when it comes to dissemination in time and space.

With a population-based study (2015-2022),[32] we derived current MS incidence trends by applying a validated algorithm to administrative data from ~60,000,000 persons in Germany. MS incidence (and sex ratio) remained stable over the eight years of study. However, the cumulative incidence per 100,000 persons declined slightly over the study period, which may have been influenced by immigration and/or a growing population as well as a shortened lag time of diagnosis driven by the higher sensitivity of the updated diagnostic criteria released in 2017.

After receiving an MS diagnosis, patients are commonly recommended by a physician to start a DMD treatment. As with all drugs, these DMDs carry risk of ADR, such as an infection. Fortunately, there are measures to mitigate the risk of an infection, such as the use of vaccinations before starting a DMD. However, these complex diagnostic screening measures pose an everyday challenge in MS patient care. Today, screening for infections in MS patients is considered essential. However, the clinical relevance and frequency of each individual infection screened for remains uncertain in the real-world setting. In order to address this knowledge gap, in collaboration with the University Hospital Münster, we conducted a multicenter study between 2014 and 2016 focusing on these screening measures[33]: Infectious risk stratification was performed in patients with immune-mediated neurological diseases (i.e., MS and neuromyelitis optica spectrum disorders [NMOSD]) before the initiation of a potent DMD. Of note, 177 patients were tested with an IFN-γ release assay (IGRA) in Münster and Düsseldorf; 7 patients had a reactive result (3.95% [95% confidence interval: 2–8%]) and were therefore diagnosed with a latent tuberculosis infection (LTBI). Consequently, these patients with LTBI received the required 3 (multi-antibiotic) or 9 months (single antibiotic) treatment regime. This extensive course of antibiotics can be

highly burdensome on patients, and in our study two of the diagnosed patients developed a significant ADR after LTBI treatment was administered. Fortunately, none of the patients who underwent antibiotic treatment developed an active tuberculosis infection (routine follow-up tuberculosis testing normal). Further, of the 102 patients screened for Varicella zoster virus (VZV) in Düsseldorf, 3 (2.9% [95% confidence interval: 0.6–8.4%]) patients presented findings indicating a lack of immunity (VZV IgG <100.0 IU/mL) while all 78 patients from Münster showed immunity against VZV. Given that a VZV infection is considered serious in e.g. fingolimod treated patients[34], a vaccination is warranted when a lack of immunity is present. Of the total of 159 patients screened for hepatitis B, 3 patients were tested positive for anti-HBc-IgG which indicates recovery and immunity after a previous hepatitis B infection (1.9% [95% confidence interval: 0.4–5.4%]). This screening measure is crucial for patients considering a B cell depleting therapy by anti-CD20 monoclonal antibodies given that e.g. rituximab (a commonly used [off-label] DMD for MS with a comparable mode of action as the on-label MS DMDs ocrelizumab, ofatumumab and ublituximab) increases the risk of a fulminant hepatitis B reactivation in anti-HBc-IgG-positive patients.[35]

To summarize, screening for infectious diseases, despite being onerous, should be performed before embarking on DMD in order to mitigate treatment associated risks.

2.2 Chronic Inflammatory Demyelinating Polyneuropathy

This chapter is based on the following Original Research articles:

Ingwersen J, Graf J*, Kluge J, Weise M, Dietrich M, Lee J-I, Harmel J, Hartung H-P, Ruck T, Meuth SG, Albrecht P, Aktas O, Ringelstein M. CNS Involvement in Chronic*

Inflammatory Demyelinating Polyneuropathy: Subtle Retinal Changes in Optical Coherence Tomography. Neurol Neuroimmunol Neuroinflamm. 2022;9(1).

*doi:10.1212/NXI.0000000000001099 - *equally-contributing authors*

Graf J, Jansen L, Ingwersen J, Ringelstein M, Harmel J, Rybak J, Kolbe R, Rhöse L, Gemerzki L, Lee J-I, Klistorner A, Guthoff R, Hartung H-P, Aktas O, Albrecht P. Multifocal visual evoked potentials in chronic inflammatory demyelinating polyneuropathy. Ann Clin Transl Neurol. 2018;5(8):952-961.

doi:10.1002/acn3.593

In clinical practice, diagnosing rare or orphan diseases remains a challenge. However, while each rare disease is rare, patients with rare diseases as a collective are numerous. A recent call for action challenges the medical community to coordinate efforts in order to define rare and orphan diseases more precisely.[36] Use of state-of-the art, non-invasive diagnostic tools suitable for the diagnosis of patients with rare diseases would be a major advancement and help address this call to action. CIDP is a rare immune-mediated disease (e.g., prevalence rate of 2.84 per 100,000 in England[37] and annual incidence of 0.3 per 100,000 in Iceland[38]) characterized by symmetrical neuropathic symptoms which progress and/or relapse over a course of at least 2 months.[39,40] Given that there are 'typical' and 'atypical' clinical subtypes, diagnosing this rare disease in a timely manner is particularly challenging.[41] We have conducted two cross-sectional, prospective studies at the University Hospital of Düsseldorf applying the state-of-the art, non-invasive tools optical coherence tomography (OCT)[42] and multifocal visual evoked potentials (mfVEP)[43] for use in CIDP

patients in order to define this disease more precisely. Applying these diagnostic tools of the visual pathway is of particular interest given that previous studies suggest an involvement of the central nervous system in CIDP patients.[44,45] In both Düsseldorf studies, CIDP patients were compared with age- and sex-matched healthy controls (OCT: 22 CIDP patients versus 22 healthy controls; mfVEP: 18 CIDP patients versus 18 healthy controls). Briefly, while the OCT examination revealed subtle evidence for retinal degeneration in CIDP patients versus healthy controls, mfVEP measurements did not differ between the groups. These findings warrant corroboration in larger, independent CIDP patient cohorts in future studies.

2.3 Moyamoya Angiopathy

This chapter is based on the following Original Research article:

Graf J, Schwitalla JC*, Albrecht P, Veltkamp R, Berlit P, Hartung H-P, Aktas O, Kraemer M. Misdiagnoses and delay of diagnoses in Moyamoya angiopathy-a large Caucasian case series. J Neurol. 2019;266(5):1153-1159.*

*doi:10.1007/s00415-019-09245-9 - *equally-contributing authors*

The relevance of misdiagnoses and delay in the diagnoses in rare diseases have been highlighted in a retrospective analysis we have conducted in collaboration with the Alfried Krupp Hospital Essen using a large Caucasian case series of patients with MMA.[46] The rare arteriopathy MMA is characterized by non-inflammatory occlusion or stenosis of intracranial arteries, leading to manifest or transient ischemic events of the brain.[47] This analysis was based on a monocentric chart review of the Alfried Krupp Hospital Essen, a European Reference Network center known for its longstanding

expertise in diagnosing and treating patients with MMA.[48-50] Delay of MMA diagnosis has been assessed in 187 patients: The diagnosis was delayed ≥1 year in 106/187 patients (56.7%). Of note, the mean delay in diagnosis from symptom onset was 5.28 (standard deviation 5.11) years. Misdiagnosis has been assessed in 192 patients: Only 38% of patients instantly received a correct diagnosis at the first clinic visit. Our systematic analysis of a large case series underscores both the high frequency of misdiagnosis and the delay of diagnosis in patients affected by MMA. This circumstance may impede a timely, adequate treatment.[49,50]

2.4 Aseptic Meningitis Epidemic

This chapter is based on the following Original Research article:

Graf J, Hartmann CJ*, Lehmann HC, Otto C, Adams O, Karenfort M, Schneider C, Ruprecht K, Bosse HM, Diedrich S, Böttcher S, Schnitzler A, Hartung H-P, Aktas O, Albrecht P. Meningitis gone viral: description of the echovirus wave 2013 in Germany. BMC Infect Dis. 2019;19(1):1010.*

*doi:10.1186/s12879-019-4635-6 - *equally-contributing authors*

The diagnostic workup of a patient suspicious for meningitis presenting with headache, fever and neck stiffness at an emergency department poses an everyday challenge: a timely, accurate diagnosis is warranted given that a misdiagnosis may lead to serious consequences.[51] However, when a causative agent for meningitis cannot be determined by cerebrospinal fluid culture, the patient most likely suffers from an aseptic meningitis.[52] The most common cause of aseptic meningitis is a viral infection.[53,54] Evidence suggests that the causative agent remains unknown in ~20% of patients with

meningitis or encephalitis.[53] This uncertainty complicates patient care, especially during seasonal aseptic meningitis surges. We have conducted a retrospective, multicenter study at the University Hospitals of Düsseldorf, Cologne and Berlin, Germany, which described the enterovirus epidemic in Germany in 2013.[55] In this study, 72 enterovirus-positive cases (median age of 15 [interquartile range 3.25; 32.75] years, 31 females [43.1%]) and 45 enterovirus-negative (median age of 36 [interquartile range 28; 48.5] years, 16 females [35.6%]) cases were identified and compared. In 2013, enterovirus-positive cases peaked in this study cohort in July (n=20) and August (n=28). Of note, patients with enterovirus-positive meningitis spent relatively few nights in hospital compared to enterovirus-negative patients (3 [interquartile range 1; 5] versus 6 [interquartile range 3; 13] nights, adjusted $p < 0.01$, Mann-Whitney *U* test). There were no fatal cases in any group. Nevertheless, aseptic meningitis epidemics regardless of the cause are associated with considerable costs for society given the high case numbers, the loss of work due to sick leave and the necessary resources for medical treatment. The study suggests that enterovirus-positive cases usually present with a more benign disease course and a shorter hospitalization period, compared to enterovirus-negative cases.

3. Therapeutic Challenges in Neurological Diseases

3.1 Multiple Sclerosis

This chapter is based on the following Original Research articles:

Graf J, Leussink VI*, Soncin G*, Lepka K, Meinl I, Kümpfel T, Meuth SG, Hartung H-P, Havla J, Aktas O, Albrecht P. Relapse-independent multiple sclerosis progression under natalizumab. Brain Commun. 2021;3(4):fcab229.*

*doi:10.1093/braincomms/fcab229 - *equally-contributing authors*

The following three population-based studies performed during a 1.5-year postdoctoral research fellowship at the University of British Columbia, Vancouver, Canada were funded by the German Research Foundation (DFG). This research was made possible by a personal DFG grant (applicant: Dr. med. Jonas Graf; project number: 438899010).

Ng HS, Graf J*, Zhu F, Kingwell E, Aktas O, Albrecht P, Hartung H-P, Meuth SG, Evans C, Fisk JD, Marrie RA, Zhao Y, Tremlett H. Disease-Modifying Drug Uptake and Health Service Use in the Ageing MS Population. Front Immunol. 2021;12:794075.*

*doi:10.3389/fimmu.2021.794075 - *equally-contributing authors*

Graf J, Ng HS, Zhu F, Zhao Y, Wijnands JM, Evans C, Fisk JD, Marrie RA, Tremlett H. Disease-modifying drugs, multiple sclerosis and infection-related healthcare use in British Columbia, Canada: a population-based study. Lancet Reg Health Am. 2024;29:100667.

doi:10.1016/j.lana.2023.100667

Graf J, Ng HS, Zhu F, Zhao Y, Wijnands JM, Evans C, Fisk JD, Marrie RA, Tremlett H. Emergency department use by persons with MS: A population-based descriptive study with a focus on infection-related visits. Mult Scler. 2022;28(11):1825-1828.

doi:10.1177/13524585221078497

MS is a chronic, immune-mediated disease of the brain and spinal cord which may present with a relapsing and/or progressive clinical phenotype. Some MS patients with a relapsing disease course develop a secondary progressive course over time.[56] However, more and more evidence suggests that the clinical course of MS is perhaps best described as a continuum.[57] Treating patients with secondary disease progression remains challenging despite available treatment options.[58] We have conducted a retrospective chart review study in collaboration with the Institute of Clinical Neuroimmunology, Ludwig-Maximilians University Hospital, Munich, Germany, which assessed the relevance of the development of a secondary progressive disease course in MS patients treated with the monoclonal antibody natalizumab.[59] Natalizumab may very effectively reduce relapse rates, however, its effect on the transition to a secondary progressive diseases course remains uncertain.[60,61] As a proxy for the onset of secondary progressive disease the recently developed concept of confirmed progression independent of relapse activity (cPIRA) in combination with the Expanded Disability Status Scale (EDSS) reference score was applied. The EDSS is a clinical assessment of quantifying disability in MS patients. For inclusion, a natalizumab treatment duration of at least 24 months was required (detailed inclusion/exclusion criteria may be found elsewhere[59]).

The study outcome of cPIRA was defined as a ≥12 week confirmed disability progression independent of a clinical relapse. This outcome was evaluated in all

patients including those who discontinued natalizumab therapy in the follow-up. Disability progression was defined as an EDSS worsening (increase) of 1 point in patients with an EDSS ≤3 at baseline or a half point increase in patients with a baseline EDSS ≥3.5 using a roving EDSS reference score, as described elsewhere.[62] Of all 184 natalizumab-exposed patients included, 140 patients (median age at natalizumab onset 33.5 years; 92 [65.7%] female) presented as relapsing (76%), while 44 (median age at natalizumab onset 38.5 years; 26 [59.1%] female) developed cPIRA as an indicator for secondary progressive multiple sclerosis (24%). cPIRA occurred after a mean time of receiving natalizumab of 10 (standard deviation 1) years. MS patients who developed cPIRA with and without superimposed relapses as well as relapsing remitting multiple sclerosis patients with relapse-associated worsening presented with a mean deterioration of 1.5 (standard deviation 0.9) EDSS points. This study, which was limited by its retrospective design, highlights the challenge of managing MS patients receiving long-term treatments: close monitoring of clinical disability is warranted. A major strength of this study was the long observational period (median natalizumab therapy duration ~5 years), which would be challenging in a phase 3 trial. Our findings suggest that preventing relapses does not automatically prevent the onset of a secondary diseases course.

Other therapeutic challenges in MS are the treatment of the ageing population as well as balancing the risk of DMD-associated infection. The effectiveness of the DMDs in the older (age ≥55 years) MS population and the relevance of infections in long-term DMD treatment remains uncertain. A recent multicenter, randomized non-inferiority clinical trial assessing DMD discontinuation in MS cases ≥55 years of age suggests that discontinuation may be a reasonable option for patients with a stable disease.[63] However, this clinical trial also suggests that DMD discontinuation may increase the risk of new magnetic resonance imaging activity in brain and spinal cord.[63] We have

assessed the effectiveness of DMDs in the ageing population in a population-based study in British Columbia (BC), Canada.[64] In order to tackle this challenging question, the linked health administrative data from BC, Canada, which has been prospectively captured from 1996 to 2017, has been accessed.

A validated algorithm was used in order to identify persons with MS requiring at least three International Classification of Diseases (ICD) codes for MS (ICD 9/10: 340/G35) from the hospital or physician claims datasets, or at least one prescription filled for an MS DMD.[65] The date of the first MS-specific or demyelinating disease-related ICD code, or DMD prescription filled was the index date, and persons with MS were eligible for inclusion if they were 18 years or older and resident in BC for at least 1 year before the index date. Detailed methods and cohort characteristics can be found elsewhere.[64]

At the index date, 78.7% (15,235/19,360) of persons with MS were aged <55 years and 21.3% (4,125/19,360) were ≥55 years. Of those aged <55 years at the index date, 29.7% (4,526/15,235) filled a DMD prescription during follow-up, whereas 5.0% (206/4,125) of persons aged ≥55 years at the index date did so. Our analysis of prospectively collected health administrative data revealed beneficial effects of the MS DMDs on hospitalizations for those MS cases aged <55 at the time of exposure. However, for DMD exposed persons with MS ≥55 years of age, the hospitalization hazard was not significantly lowered. This population-based study enhances the overall comprehension of the potential advantages and risks associated with DMD use in the ageing MS population.

Further, infection-related healthcare use in DMD exposed versus unexposed persons with MS has been assessed in another population-based study we have conducted using the same cohort from BC, Canada, as already described above.[66]

Briefly, 19,360 persons with MS living in BC, Canada (1996 to 2017) were identified, of whom 13,940 (72.0%) were women. The mean follow-up time (MS index date until study end) was similar between those who did and those who did not fill a DMD prescription, with the mean being 11.7 (standard deviation 7.3) years for the entire group. The mean age at index date was 44.5 (standard deviation 13.3) years. Overall, 4,732 (24.4%) persons filled at least one MS DMD prescription. Persons never (versus ever) filling a DMD prescription were, on average, older at the index date (46.9 [standard deviation 13.7] versus 37.1 [standard deviation 9.8] years), and had a higher comorbidity burden, while the distribution of socioeconomic status quintiles was similar between the two groups.

Relative to no DMD, any DMD exposure was associated with a 12% lower adjusted rate ratio (aRR) of infection-related physician claims (aRR=0.88; 95% confidence interval: 0.85-0.92). a 36% lower adjusted hazard ratio (aHR) of infection-related hospitalizations (aHR=0.64; 95% confidence interval: 0.56-0.73) and a 14% higher rate ratio of infection-related prescription fills (aRR=1.14; 95% confidence interval: 1.08-1.20).

Little is known about emergency department visits by persons with MS. Interestingly, a descriptive, population-based study (BC, Canada) which we have conducted focusing on infection-related emergency department visits did not reveal a difference in proportion of persons with MS ever versus never using a DMD to treat MS.[67] The above-mentioned population-based studies were limited by the inability to examine the more recently approved DMDs. Further, clinical data, such as the MS disease course/severity/activity, or lifestyle-related information like alcohol consumption or smoking could not be assessed.

All in all, the above-mentioned real-world population-based studies filled major knowledge gaps as DMDs are usually only tested in highly regulated trials over 2-3 years before market approval. MS DMD exposure was associated with differences in infection-related healthcare use. Infection-related hospitalizations and physician visits were lower. However, prescription fills were higher. These differences in infection-related healthcare use warrants consideration.

3.2 Diseases treated with Intravenous Immunoglobulin

This chapter is based on the following Original Research article:

Graf J, Ingwersen J, Lepka K, Albrecht P, Hartung H-P, Ringelstein M, Aktas O. Factors associated with headache in intravenous immunoglobulin treatment for neurological diseases. Acta Neurol Scand. 2019;140(4):290-295.

doi:10.1111/ane.13144

Intravenous immunoglobulin treatment (IVIg) is an established, generally well-tolerated treatment[68] in e.g. CIDP patients. However, patients receiving IVIg may develop cephalgia, or even present with an aseptic meningitis.[69] The factors associated with cephalgia in IVIg treatment remain poorly understood. Therefore, we have conducted a retrospective chart review study which analyzed the occurrence of cephalgia in 91 IVIg infusions in 67 patients (20 females [29.9%]; 19 patients received more than one IVIg infusion).[70] Cephalgia was documented after 24.2% (22/91) of infusions in 15 of 67 (7 female, 8 male) individual patients (22.4%). The mean age of all 67 patients was 64.6 [standard deviation 11.7] years; descriptively, the 15 patients developing cephalgia were younger (mean age 59.0 [standard deviation 11.1] years), compared

to 57 patients without cephalgia (mean age 65.4 [standard deviation 11.8] years). A stepwise forward binary logistic regression analysis including baseline systolic as well as diastolic blood pressure, baseline heart rate, baseline body temperature, infusion duration, infusion rate, dosage, age, and sex was performed in order to assess factors that may influence the occurrence of cephalgia post-IVIg infusion. Here, higher baseline systolic blood pressure (p = 0.017) influenced headache the most, followed by age (p = 0.029). This study was limited by its retrospective design. However, given that body temperature was not associated with cephalgia, a systematic immune response after IVIg infusion may not be a major influence in developing cephalgia.

3.3 Moyamoya Angiopathy

This chapter is based on the following Original Research articles:

Kraemer M, Karakaya R, Matsushige T, Graf J, Albrecht P, Hartung H-P, Berlit P, Laumer R, Diesner F. Efficacy of STA-MCA bypass surgery in moyamoya angiopathy: long-term follow-up of the Caucasian Krupp Hospital cohort with 81 procedures. J Neurol. 2018;265(10):2425-2433.

doi:10.1007/s00415-018-9031-4

Kraemer M, Sassen J, Karakaya R, Schwitalla JC, Graf J, Albrecht P, Hartung H-P, Diehl RR, Berlit P, Laumer R, Diesner F. Moyamoya angiopathy: early postoperative course within 3 months after STA-MCA-bypass surgery in Europe-a retrospective analysis of 64 procedures. J Neurol. 2018;265(10):2370-2378.

doi:10.1007/s00415-018-8997-2

Performing randomized-controlled trials in rare disease patients constitutes a significant challenge. Retrospective, real-world analyses may be considered an adequate tool to inform treatment planning for patients with a rare disease, such as MMA. Two retrospective chart review studies performed in collaboration between the University Hospital Düsseldorf and the European Reference Network center Alfried Krupp Hospital Essen, Germany, assessed the clinical outcome of bypass surgery between the superficial temporal artery and the middle cerebral artery (STA-MCA) in Caucasian patients with MMA over the short-term (64 direct bypass procedures in 45 patients; 34 [75.6%] females; mean age at time of first surgery 41.8 [standard deviation 13.68] years)[50] and long-term (81 STA-MCA bypass procedures in 54 patients; 39 [72.2%] females; mean age at the time of first surgery 39.1 [standard deviation 12.8] years)[49]. Regarding hemodynamic compromised stages of MMA in patients with Asian ethnicity, there is a consensus that STA-MCA may be beneficial.[71,72] However, evidence in Caucasian patients is scarce.

Over the short-term[50], after 15% (10/64) of STA-MCA procedures MMA patients complained of clinical symptoms excluding postoperative pain and headaches. Radiological imaging revealed subdural hematoma in 70% (7/10) of MMA patients.

After 3 months, no persisting clinical symptoms were reported in 98.4 % (62/63) of procedures (due to living abroad, one patient was lost to follow-up). After one procedure (1.6%), a persisting worsening of aphasia most likely influenced by a generalized seizure was reported. No new magnetic resonance imaging lesion has been detected in this case in comparison with the preoperative magnetic resonance imaging.

Over the long-term[49], none of the MMA patients receiving STA-MCA experienced new symptoms related to stroke or haemorrhage nor any new pathologic features were

evident on magnetic resonance imaging for 38.2 months. Further, after 37.2 months, magnetic resonance angiography revealed a reduction of MMA collaterals in 83.3% (65/79) hemispheres. These chart reviews are limited by their retrospective design.

All in all, evidence from these retrospective chart reviews suggests that STA-MCA is both a safe and an effective procedure in Caucasian MMA patients.

4. Conclusion

The diagnostic and treatment landscape in neurology is becoming progressively complex. Today in clinical neurology, for example, screening for a potential risk factor before starting a treatment (e.g. LTBI screening in MS patients) may lead to long-term antibiotic treatment, which is again associated with a therapeutic risk. Our work focusing on infectious risk stratification underscores the relevance of this complexity in everyday routine practice. Further, in the future, state-of-the-art, non-invasive diagnostic tools (e.g. optical coherence tomography and multifocal visual evoked potentials) may be able to help to further differentiate diseases of the peripheral nervous system. The findings derived from the above-mentioned real-world and population-based studies filled major knowledge gaps as drugs used to treat multiple sclerosis are usually only tested in highly regulated trials over 2-3 years before market approval. Further, these studies narrowed down the relevance of misdiagnoses (MMA) and disease severity (aseptic meningitis) in rare diseases which cannot be feasibly investigated with randomized-controlled trials.

All in all, major health care challenges of the 21st century need to be addressed with observational, cohort and/or population-based studies, which can neither ethically nor feasibly be solved with short-term or costly randomized-controlled clinical trials. For example, diagnostic procedures and/or population-based analyses may one day foresee the development of certain diseases in persons at risk. Earlier diagnosis and treatment may set the path for a prevention of progression in chronic diseases. This way, doing no harm in medicine may become less of a challenge when balancing safety, risk and benefits of clinical decisions will be enabled and informed by population-based research and state-of-the-art diagnostic tools.

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Key: Dr. med. Jonas Maximilian Graf contributed to the publications marked in **bold**.

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Eidesstattliche Versicherung

Ich versichere an Eides statt, dass ich die vorliegende Habilitationsschrift eigenständig angefertigt habe und die zugrundeliegende wissenschaftliche Leistung eigenständig erbracht habe.

Ich erkläre, dass bei den wissenschaftlichen Untersuchungen, die Gegenstand der schriftlichen Habilitationsleistung sind, ethische Grundsätze und die Grundsätze und Empfehlungen zur Sicherung guter wissenschaftlicher Praxis beachtet wurden.

Ich erkläre, dass keine weiteren Habilitationsverfahren eingeleitet oder erfolglos beendet wurden.

Dr. med. Jonas Maximilian Graf

Düsseldorf, den 06.01.2025

Appendix

ANNALS of Clinical and Translational Neurology
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BRIEF COMMUNICATION

Infectious risk stratification in multiple sclerosis patients receiving immunotherapy

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Abstract

The increasing number of potent treatments for multiple sclerosis warrants screening for infections. To investigate the prevalence of infections in two independent German patient cohorts with multiple sclerosis/neuromyelitis optica spectrum disorders (NMOSD), we performed a retrospective chart review study of multiple sclerosis/NMOSD patients who underwent testing for infections between 2014 and 2016. We show that 6 out of 80 tested patients (Düsseldorf cohort) and 2 out of 97 tested patients (Münster cohort) had a latent tuberculosis infection; total 3.95%, 95% CI: 2–8%. Our findings suggest that latent tuberculosis infection is frequent (>1%). Screening should be performed before embarking on immunomodulatory therapies to allow treatment and mitigation of the risk of a reactivation.

Introduction

Balancing benefit and risk in modern multiple sclerosis (MS) drug management is crucial. In this context, the reactivation or de novo acquisition of infectious diseases is gaining relevance.[1,2]

This study focuses on the significance of screening for latent tuberculosis infection (LTBI) in MS patients. The possible implications of LTBI have already been reviewed[1,3] but there is a paucity of real-world data including tuberculosis (TB) risk stratification.

Patients and Methods

We conducted a bicentral retrospective chart review study at the MS Centers of the Heinrich-Heine-University Düsseldorf and the University Hospital of Münster. In Düsseldorf, we searched for all MS/NMOSD patients to be started on highly potent immunotherapy between May 2014 and December 2016, while in Münster all patients to be started on dimethyl fumarate or alemtuzumab were investigated between May 2014 and December 2016. In Münster, comprehensive screening for infectious risks was only performed for the cohorts of patients on alemtuzumab and dimethyl fumarate, and only patients with comprehensive screening were included to avoid a selection bias. Thus, from Münster only patients from these cohorts were enrolled. Screening was performed as follows: Tuberculosis (T-Spot.TB Test, Oxford Immunotec (Düsseldorf/Münster)), human immunodeficiency virus (HIV; HIV Ag/Ab Combo, 4J27-30, Abbott (Düsseldorf); ADVIA Centaur HIV Ag/Ab Combo, CHIV, Siemens

Healthcare (Münster)), hepatitis B (HBsAg qualitative II, 2G22-30 and Anti-HBc II, 8L44-30, Abbott (Düsseldorf); ADV IA Centaur HBsAgII HBsII-Test and ADVIA Centaur-HBc-gesamt-Test, Siemens Healthcare (Münster)), hepatitis C (Anti-HCV, 6C37-30, Abbott (Düsseldorf); ADVIA Centaur HCV-Test, aHCV, Siemens Healthcare (Münster)), *Varicella zoster* virus (VZV; Liaison VZV IgG, Fa. DiaSorin (Düsseldorf/Münster)), *Treponema pallidum* (Treponema CLIA, Liaison Treponema Screen, Fa. DiaSorin (Düsseldorf); TPPA/FTA/RPR IFT, Mast Diagnostica (Münster)), and *John Cunningham* polyomavirus (JCV, Stratify® assay (Düsseldorf/Münster)). The study was approved by the ethics committee in Düsseldorf (registry number 5598).

Results

Results of virological, *Treponema pallidum* and IFN-γ release assay (IGRA) testing

Of the 80 IGRA-tested patients in Düsseldorf, 58 (72.5%) were female and 22 (27.5%) were male. Mean age was 41.9 years. The patients were diagnosed with RRMS (52; 65%), SPMS (19; 23.7%), PPMS (6; 7.5%), and NMOSD (3; 3.8%). Mean EDSS was 4. IGRA testing (Table S1) revealed a reactive result in 6 of 80 (7.5%, 95% CI: 3–16%) patients (patients *D2, D20, D21, D33, D40, D80)*. Active TB was ruled out by routine blood work-up, chest X-ray, microbiological testing of sputum, and urine. LTBI treatment was performed according to the recommendations of the Centers for Disease Control and Prevention (CDC)[4] or Blumberg et al.[5] IGRA testing revealed a borderline result in 3 of 80 (3.8%, 95% CI: 0.8–11%) patients. All retests after 3–4 weeks were negative.

All patients in Düsseldorf who underwent screening for hepatitis B/C, HIV, and *Treponema pallidum* were tested negative for an acute infection or a prior exposure to the pathogen. The presence of anti-HBc-IgG indicating recovery and immunity after a previous hepatitis B infection was detected in one patient. Of the 102 patients screened for VZV, 3 (2.9%) patients presented findings indicating a lack of immunity against the virus (VZV IgG <100.0 IU/mL). Of all patients tested for JCV serostatus (n = 430), 139 were negative, 72 were positive with an index value <0.9, 51 were positive with an index value 0.9–1.5, and 168 were positive with an index value of >1.5. No case of progressive multifocal leukoencephalopathy (PML) occurred during the observation period at the MS center in Düsseldorf. An overview of the Düsseldorf cohort results is provided in Table 1.

To investigate whether the rather high LTBI rate in the Düsseldorf cohort might have been specific to Düsseldorf, the capital of the federal state of North Rhine Westphalia which is located in the largest urban industrial area of Germany, we chose to also investigate the LTBI rates in Münster, a smaller city located in the more rural area of Westphalia. Of the 97 IGRA-tested MS patients (96 RRMS, 1 SPMS) in Münster, 57 (58.8%) were female and 40 (41.2%) were male. Mean age was 35.8 years. Mean EDSS was 2.45. In this cohort, we identified one reactive case (*M97*; 1%, 95% CI: 0.01–6%) and obtained one

Table 1. Results of virological, *Treponema pallidum* and IGRA testing, Düsseldorf cohort.

Pathogen	Test used	Number of tests	Results
TB	IGRA (T-Spot)	80	71 not reactive (88.7%) 3 borderline (3.8%) 6 reactive (7.5%)
Hepatitis B	HBsAg, Anti-HBc-IgG CMIA	71 HBsAg 63 Anti-HBc-IgG	71 HBsAg negative (100%) 62 Anti-HBc-IgG negative (98.4%) 1 Anti-HBc IgG positive (1.6%)
Hepatitis C	CLIA	72	All negative
HIV	CLIA	43	All negative
VZV	VZV IgG CLIA	102	99 positive (97.1%) 3 VZV IgG <100.0 IU/mL (2.9%)
T. pallidum	CLIA	41	All negative
JCV	Stratify® assay	430	139 negative (32%) 72 positive with index value <0.9 (17%) 51 positive with index value 0.9–1.5 (12%) 168 positive with index value >1.5 (39%) 0 PML cases during observational period

TB, tuberculosis; IGRA, IFN-γ release assay; CMIA, carbonylmetalloimmunoassay; CLIA, chemoluminescence immunoassay; HIV, *Human Immunodeficiency* virus; VZV, *Varicella zoster* virus; *T. pallidum*, *Treponema pallidum*; JCV, *John Cunningham* polyomavirus; PML, progressive multifocal leukoencephalopathy.

borderline result (*M59*) and one reactive result (*M49*) which were both later refuted by negative results in the confirmation test (Table S2). Active TB was ruled out and treatment was performed as described above. In Münster, all patients who underwent screening for hepatitis B/C, HIV, and *Treponema pallidum* were tested negative for an acute infection or a prior exposure to the pathogen. The presence of anti-HBc-IgG indicating recovery and immunity after a previous hepatitis B infection was detected in two patients and all patients screened for VZV presented findings indicating immunity. Of all patients tested for JCV serostatus ($n = 68$), 22 were negative, 6 were positive with an index value <0.9, 4 were positive with an index value 0.9–1.5, 22 were positive with an index value of >1.5, and 14 were positive with an unknown index value. Two cases of progressive multifocal leukoencephalopathy (PML) occurred during the observation period at the MS center in Münster.

An overview of the Münster cohort results is provided in Table 2.

In total, of 177 patients tested with an IGRA in Düsseldorf and Münster, 7 had a reactive result (3.95%, 95% CI: 2–8%).

LTBI treatment

After testing positive, patients *D20*, *D21*, *D33, and D80* received rifampicin (RMP) 600 mg/d plus isoniazid (INH) 300 mg/pyridoxine 10–25 mg/day for 3 months and patients *D2* and *D40* received INH 300 mg/pyridoxine 20 mg/day for 9 months. Patient *M97* declined treatment.

Patients *D21*, *D33*, and *D80* in the RMP/INH/pyridoxine group received the medication continuously for 3 months, patient *D20* due to poor tolerability (dizziness, nausea) was switched to a 9-month INH 150 mg/pyridoxine 20 mg per day regimen. In parallel, patient *D20* started alemtuzumab therapy after 1 month of TB therapy.

Patient *D2* switched from INH 300 mg/pyridoxine 20 mg/day to a 6-month RMP 600 mg/pyrazinamide (PZA) 750 mg/day regimen due to paresthesia of both legs. Since the paresthesia remitted a few days after stopping INH, nerve conduction studies for isoniazid-induced polyneuropathy were not performed. In parallel, this patient was started on off-label rituximab and after completing the 6-month TB therapy, switched to alemtuzumab. Patient *D40* was also started on a rituximab therapy parallel to LTBI therapy. After completion of TB treatment, diagnostic work-up (routine blood work-up, chest X-ray, microbiological testing of sputum and urine) revealed no evidence of TB reactivation in any of the six patients. A follow-up IGRA after treatment remained – as expected – reactive.

An overview of the diagnostic work-up and treatment is provided in Figure 1.

Discussion

LTBI is the most prominent infectious risk factor besides JCV in our cohorts. We observed an expected[6] number of patients with LTBI. Due to the high awareness of the risk for developing a progressive multifocal leukoencephalopathy (PML) in the context of highly active MS therapy,

Table 2. Results of virological, *Treponema pallidum* and IGRA testing, Münster cohort.

Pathogen	Test used	Number of Tests	Results
TB	IGRA (T-Spot)	97	95 not reactive (98%) 1 borderline (1%) 1 reactive (1%)
Hepatitis B	HBsAg, Anti-HBc-IgG CLIA	96 HBsAg 96 Anti-HBc-IgG	96 HBsAg negative (100%) 94 Anti-HBc-IgG negative (98%) 2 Anti-HBc IgG positive (2%)
Hepatitis C	CLIA	97	All negative
HIV	CLIA	97	All negative
VZV	VZV IgG CLIA	78	All positive
T. pallidum	IFT	73	All negative
JCV	Stratify® assay	68	22 negative (32.5%) 6 positive with index value <0.9 (9%) 4 positive with index value 0.9–1.5 (6%) 22 positive with index value >1.5 (32.5%) 14 positive with unknown index value (20%) 2 PML cases during observational period

TB, tuberculosis; IGRA, IFN-γ release assay; CLIA, chemoluminescence immunoassay; HIV, *Human Immunodeficiency* virus; VZV, *Varicella zoster* virus; *T. pallidum*, *Treponema pallidum*; JCV, *John Cunningham* polyomavirus; PML, progressive multifocal leukoencephalopathy.

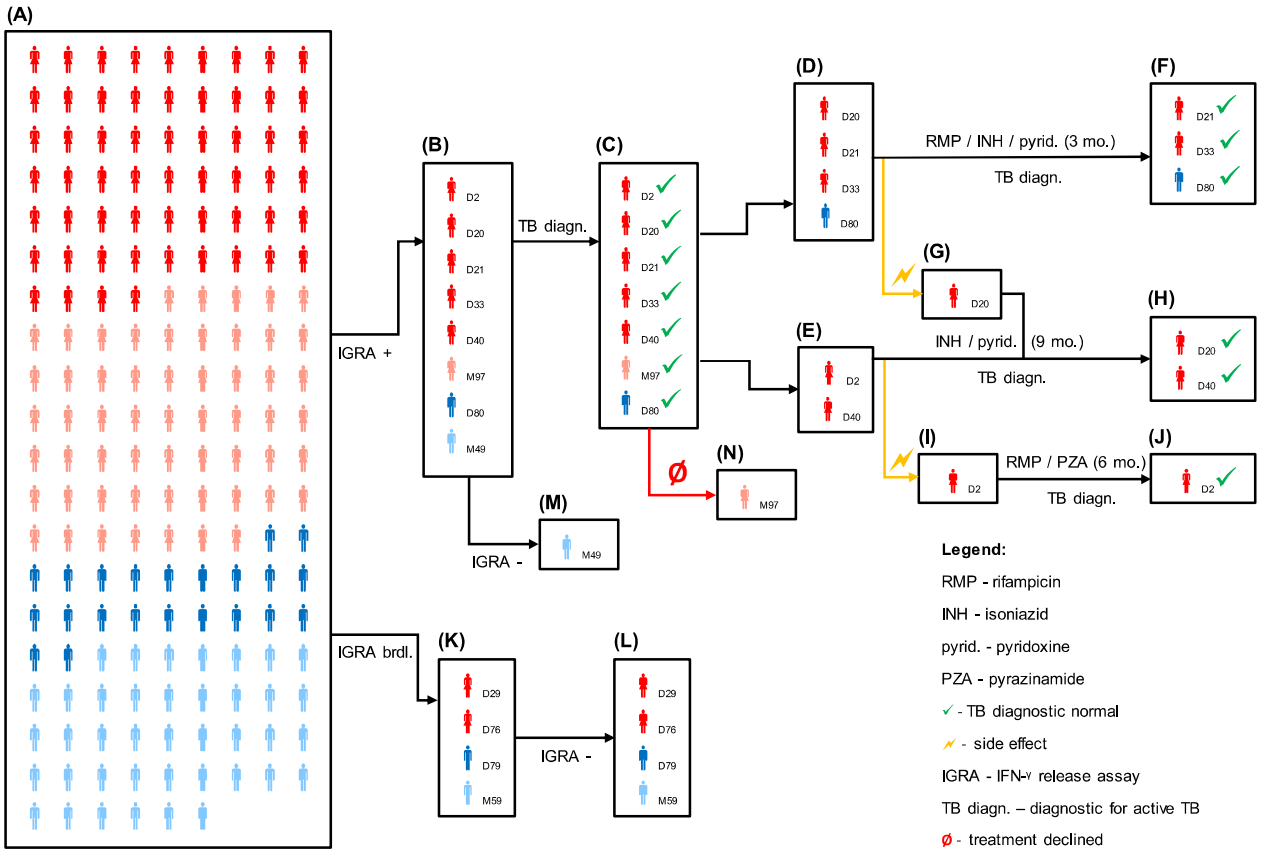

Figure 1. IGRA screening und LTBI treatment of the Düsseldorf (bold red female, bold blue male) and Münster (light red female, light blue male) cohort (lower case indicates patient ID). One hundred and seventy-seven patients were screened with an IGRA (A), eight patients had a reactive result (B). Of these eight patients with reactive IGRA, seven patients had normal routine TB diagnostic (C) and therefore LTBI and one reactive result was later confirmed as negative (M). Of these seven LTBI patients, four received RMP/INH/pyridoxine (D), two patients INH/pyridoxine (E), and one patient declined therapy (N). Of the four patients in (D), three patients continued the regime for 3 months and one patient switched to a 9-month INH/pyridoxine regime due to side effects (G). Two of the six LTBI patients started with INH/pyridoxine treatment (E), but one patient switched to a 6-month RMP/PZA regime (I) due to side effects. Routine TB diagnostic after LTBI treatment was normal (F, H, J); Four patients had a borderline (brdl.) IGRA result (K), retesting after 3–4 weeks was normal (L).

namely natalizumab, more patients have been screened for JCV antibodies. However, our data suggest that possibly also LTBI-reactivation may be a relevant risk especially in the context of highly active immunotherapies.

Clinically relevant TB infections have been associated with a number of MS treatments: While an increased risk of LTBI-reactivation has been published regarding patients treated with alemtuzumab,[7,8] daclizumab[9], natalizumab[10], and glucocorticoids,[11] fingolimod treatment was thus far not associated with an increased rate of manifest TB infections. With CD20-depleting therapies (rituximab, ocrelizumab), a more complex picture evolves: The TB infection rate does not seem to be increased in relapse-remitting[12,13] and primary-progressive[14,15] MS disease nor has this been noted in oncological patient populations undergoing extended rituximab therapy for lymphoma.[16] However, TB cases have been reported in rheumatoid arthritis patients treated with ocrelizumab in combination with methotrexate.[17]

There is a tendency toward a higher LTBI rate in Düsseldorf (7.5%) than in the independent Münster cohort (1.03%). This could be a reflection of the higher incidence of tuberculosis in Düsseldorf: In 2015, 385 cases of tuberculosis were reported in Düsseldorf and 144 in Münster (SurvStat@RKI). Thus, in our study, LTBI seems to be more relevant in the urban cohort than in the rural cohort. However, the confidence intervals of the two cohorts overlap, so a significant difference of the LTBI rate cannot be postulated. Several of our patients were already on active immunomodulatory treatments at the time of testing and some of these therapies may cause false-negative IGRA results. It is

therefore possible that the LTBI rate might even be higher. As IGRA was the primary TB test used in all patients, booster effects due to prior skin testing as common reasons of false-positive results were not an issue in our cohorts.

Three of the six IGRA-reactive patients from Düsseldorf were immigrants from countries with a higher prevalence of TB than Germany (the Balkans, Turkey, and Russia). Similarly, the patient from Münster was from Russia. The LTBI prevalence in our cohort is similar to that expected for Western Europe[6]. With regard to the current migration development in Europe, manifest tuberculosis is expected to become more relevant in patients with immunotherapy and thus LTBI screening will become more important in the future.

Real-world data from MS clinics at two German tertiary referral centers indicate that LTBI affects a relevant proportion of MS patients and is an important concern. In line with existing recommendations, screening should be performed before initiation of daclizumab and alemtuzumab treatment. According to the Rituximab Consensus Expert Committee,[18] there is no evidence to support screening patients before initiation of CD20-depleting monotherapy (rituximab, ocrelizumab). However, given the high LTBI prevalence in our cohort and the previous complications in patients with ocrelizumab combination therapy, IGRA testing may be considered when a long-term B-cell depleting therapy is planned. In patients with pertinent symptoms under immunotherapy, TB reactivation should be taken into account. Larger observational studies are needed to assess the reactivation risk in various treatment regimens and geographies.

Author Contribution

Jonas Graf – Study concept/design, acquisition/analysis/interpretation of data, drafting of the manuscript. Verena I Leussink – critical revision of the manuscript. Thomas Dehmel – critical revision of the manuscript. Marius Ringelstein – critical revision of the manuscript. Norbert Goebels – critical revision of the manuscript. Ortwin Adams – critical revision of the manuscript. Colin R MacKenzie – critical revision of the manuscript. Clemens Warnke – critical revision of the manuscript. Torsten Feldt – critical revision of the manuscript. Anna Lammerskitten – acquisition of data. Luisa Klotz – acquisition/analysis/interpretation of data, drafting and revision of the manuscript. Sven Meuth – critical revision of the manuscript. Heinz Wiendl – critical revision of the manuscript. Hans-Peter Hartung – critical revision of the manuscript. Orhan Aktas* – Study concept/design, critical revision of the manuscript. Philipp Albrecht* – Study concept/design, acquisition/analysis/interpretation of data, drafting and revision of the manuscript.

Conflict of Interest

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Table S1. Screening for Tuberculosis, detailed overview of IGRA-tested patients in Düsseldorf (D).
Table S2. Screening for Tuberculosis, detailed overview of IGRA-tested patients in Münster (M).

ARTICLE OPEN ACCESS

CNS Involvement in Chronic Inflammatory Demyelinating Polyneuropathy

Subtle Retinal Changes in Optical Coherence Tomography

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Abstract

Background and Objectives

Chronic inflammatory demyelinating polyneuropathy (CIDP) is an autoimmune disease primarily affecting the peripheral nervous system. However, several noncontrolled studies have suggested concomitant inflammatory CNS demyelination similar to multiple sclerosis. The aim of this study was to investigate an involvement of the visual pathway in patients with CIDP.

Methods

In this prospective cross-sectional study, we used high-resolution spectral-domain optical coherence tomography to compare the thickness of the peripapillary retinal nerve fiber layer and the deeper macular retinal layers as well as the total macular volume (TMV) in 22 patients with CIDP and 22 age-matched and sex-matched healthy control (HC) individuals. Retinal layers were semiautomatically segmented by the provided software and were correlated with clinical measures and nerve conduction studies.

Results

In patients with CIDP compared with healthy age-matched and sex-matched controls, we found slight but significant volume reductions of the ganglion cell/inner plexiform layer complex (CIDP 1.86 vs HC 1.95 mm^3, $p = 0.015$), the retinal pigment epithelium (CIDP 0.38 vs HC 0.40 mm^3, $p = 0.02$), and the TMV (CIDP 8.48 vs HC 8.75 mm^3, $p = 0.018$). The ganglion cell layer volume and motor nerve conduction velocity were positively associated (B = 0.002, $p = 0.02$).

Discussion

Our data reveal subtle retinal neurodegeneration in patients with CIDP, providing evidence for visual pathway involvement, detectable by OCT. The results need corroboration in independent, larger cohorts.

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Go to Neurology.org/NN for full disclosures. Funding information is provided at the end of the article.

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Glossary

CIDP = chronic inflammatory demyelinating polyneuropathy; **ETDRS** = early treatment of diabetic retinopathy study; **GCIPL** = ganglion cell IPL; **GCL** = ganglion cell layer; **GEE** = generalized estimation equation; **HC** = healthy control; **INL** = inner nuclear layer; **IPL** = inner plexiform layer; **mfVEP** = multifocal visual evoked potential; **MNCV** = motor nerve conduction velocity; **MS** = multiple sclerosis; **OPL** = outer plexiform layer; **PNS** = peripheral nervous system; **pRNFL** = peripapillary retinal nerve fiber layer; **SD-OCT** = spectral-domain optical coherence tomography.

Chronic inflammatory demyelinating polyneuropathy (CIDP) is an autoimmune disease of the peripheral nervous system (PNS) characterized by primary myelin sheath destruction and secondary axonal damage, leading to sensory and autonomic deficits, flaccid paresis, and muscle atrophy.[1] The disease usually follows a chronic progressive course with or without superimposed relapses or is relapsing, thus resembling multiple sclerosis (MS), the most common primary demyelinating autoimmune disease of the CNS. Forrester and Lascelles[2] were the first to describe 2 cases of coincident MS and inflammatory polyneuropathy in 1979. In 1987, 6 additional cases of CIDP with CNS demyelination evidenced by MRI were reported.[3] Several subsequent studies suggested CNS involvement in CIDP.[4-6] Further investigations associated CIDP specifically with visual pathway disturbance.[7-9] Holtkamp et al.[10] showed histologically optic nerve inflammation in a patient with CIDP. Japanese and Chinese groups have recently suggested the existence of a condition termed combined central and peripheral demyelination that resembles both MS and CIDP in the same patient.[11-13]

All these investigations, however, were noncontrolled studies, mainly case reports and case series. In a previous effort, investigating conductivity changes of the visual pathway in patients with CIDP using multifocal visual evoked potentials (mfVEP), we were not able to detect relevant changes compared with age-matched and sex-matched healthy individuals.[14] This finding was recently corroborated by another controlled study using full-field VEPs.[15]

Here, we investigated structural retinal changes as a marker of CNS degeneration in patients with CIDP compared with age-matched and sex-matched healthy individuals using spectral-domain optical coherence tomography (SD-OCT). OCT uses near-infrared light to generate cross-sectional and 3-dimensional images of the retina as part of the CNS. In recent years, OCT has emerged as a reliable and accurate, easy-to-access, and noninvasive technique to assess microscopic retinal pathologies, for example, in MS[16-18] and other inflammatory and degenerative CNS diseases.[19-24] In MS, spectral-domain OCT has been documented to predict long-term worsening.[25]

Methods

Patients

We performed a prospective study at the Department of Neurology, Heinrich-Heine-University Düsseldorf. Subjects were included as previously described.[14] Inclusion criteria were of age >18 years, probable or definite CIDP according to the European Federation of Neurological Societies/Peripheral Nerve Society CIDP guidelines and response to immunomodulatory treatment. The flowchart in Figure 1 gives an overview of the subject recruitment. Of 66 subjects (44 patients with probable or definite CIDP and 22 healthy subjects), 22 patients had to be excluded because of diabetes mellitus (n = 13) or concomitant ophthalmologic diseases (n = 9), such as bilateral drusen (4), cataract (2), glaucoma (1), papilledema (1), and choroidal neovascularization (1), which could confound the OCT measurements. Furthermore, 7 single eyes were excluded because of drusen (6) and macular edema (1). Healthy controls (HCs) did not report symptoms or show any clinical signs suspicious of polyneuropathy. Four subjects with CIDP revealed relevant serologic findings (3 had monoclonal gammopathy and 1 was positive for anti-myelin–associated glycoprotein immunoglobulin M antibodies). The Inflammatory Neuropathy Cause and Treatment Overall Disability Sum Score was evaluated in all subjects with CIDP as a measure of disability. Demographic parameters of the study partcipants are listed in the Table. All subjects received neuroophthalmological examinations, including tonometry, slit-lamp examination, and fundoscopy. In addition, 16 of 22 patients with CIDP (73%) were tested for corrected low contrast letter recognition using 2.5% low contrast early treatment of diabetic retinopathy study (ETDRS) charts. Because nerve conduction studies of the lower limbs showed a high rate of signal loss, the right ulnar nerve was used to investigate associations with OCT parameters. Figures 2A–C exemplify the measurement of the macular volumes by consecutive vertical scans (Figure 2A) and the peripapillary retinal nerve fiber layer (pRNFL) thickness (Figure 2B), and illustrate a cross-section through the deeper retinal layers (Figure 2C). The Strengthening the Reporting of Observational Studies in Epidemiology cross-sectional reporting guidelines were used.[26]

Spectral-Domain Optical Coherence Tomography

APOSTEL reporting recommendations were applied for the SD-OCT methodology and results.[27] The methods are well established and have also been used and described elsewhere.[22,23,28] For the RNFL assessment, using high-resolution scanning mode, we obtained 12° peripapillary, disk-centered ring scans. For macular volume evaluation, we captured 61 fovea-centered vertical scans (30° × 25°, high-speed scanning mode). The total retinal volume and the volumes of the different retinal layers were measured by applying the

standard 1-, 3-, and 6-mm ETDRS grid in macular volume scans and using the mean volume of all sectors. For SD-OCT imaging of both eyes, the SPECTRALIS OCT device (Heidelberg Engineering, Germany) with the image alignment eye-tracking software system (TruTrack and Nsite analytics, Heidelberg Engineering) was used. Averaging of macular volume scans was performed from 14 images and of peripapillary ring scans from 100 scans (automatic real time). The threshold for the image quality was beyond 20 dB. Semiautomatic segmentation of all retinal layers using the Heidelberg Eye Explorer software (version HEYEX 1.8.6.0, Viewing Module 5.8.3.0) was manually corrected by a blinded rater. For analysis, we used only scans meeting the OSCAR-IB quality control criteria.[29]

Statistical Evaluation

SPSS Statistics 24 (IBM) was used for statistical analyses. Generalized estimation equation (GEE) models correcting for sex and age and accounting for within-subject, intersegment, or intereye correlations using an exchangeable working correlation matrix were applied to analyze associations between clinical data and SD-OCT parameters and to test for differences of SD-OCT parameters between controls and patients with CIDP.

Patient Consent and Standard Protocol Approvals

This study was approved by the local ethics committee of Heinrich-Heine-University Düsseldorf (registry number 4389). In accordance with the Declaration of Helsinki, written informed consent was obtained from all study participants.

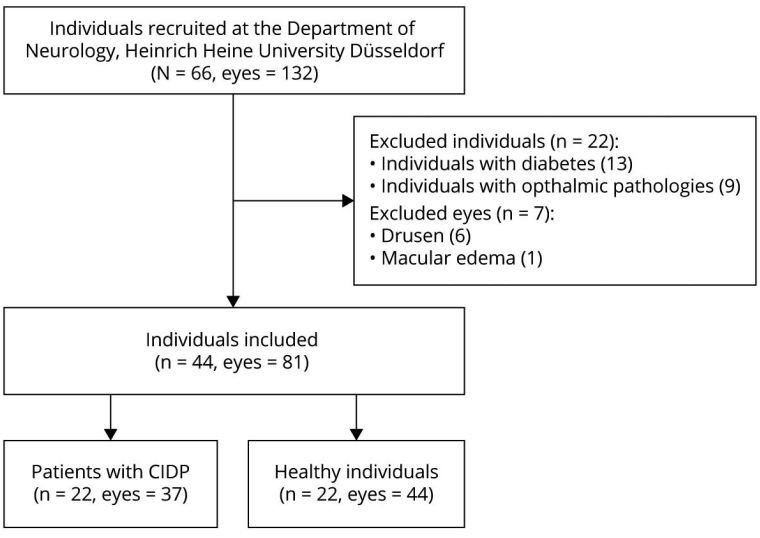
On reasonable request from any qualified investigator, anonymized data not published within this article will be made available.

Results

The mean total macular volume (TMV) was significantly reduced in patients with CIDP (8.48 mm^3, ± 0.38) compared with HCs (8.75, ± 0.37 mm^3; p = 0.018, GEE, Figure 2D). Further analyses of the different macular layers revealed a significant thinning of the ganglion cell layer (GCL) in patients with CIDP (1.03 ± 0.10 mm^3) compared with HCs (1.07 ± 0.11 mm^3, p = 0.037) and of the inner plexiform layer (IPL) in patients with CIDP (0.83 ± 0.08 mm^3) vs healthy individuals (0.88 ± 0.06 mm^3, p = 0.015). Consequently, the often-used combined ganglion cell IPL (GCIPL) volume also showed a significant difference (CIDP 1.86 ± 0.17 vs HCs 1.95 ± 0.13 mm^3, p = 0.018). Furthermore, the pigment epithelium was significantly reduced in patients with CIDP compared with HCs (0.38 ± 0.04 vs 0.40 ± 0.03 mm^3, p = 0.02). No changes were observed for the macular retinal nerve fiber layer (0.93 ± 0.15 vs 0.96 ± 0.11 mm^3; p = 0.415), the inner nuclear layer (0.99 ± 0.08 vs 0.98 ± 0.06 mm^3; p = 0.715), the outer plexiform layer (0.77 ± 0.08 vs 0.80 ± 0.07 mm^3; p = 0.067), and the outer nuclear layer (1.72 ± 0.16 vs 1.78 ± 0.23 mm^3; p = 0.758). Moreover, the peripapillary retinal nerve fiber layer (pRNFL) thickness did not differ between patients with CIDP (96.58 ± 9.55 μm) and HCs (97.37 ± 8.39 μm; p = 0.635) (Table).

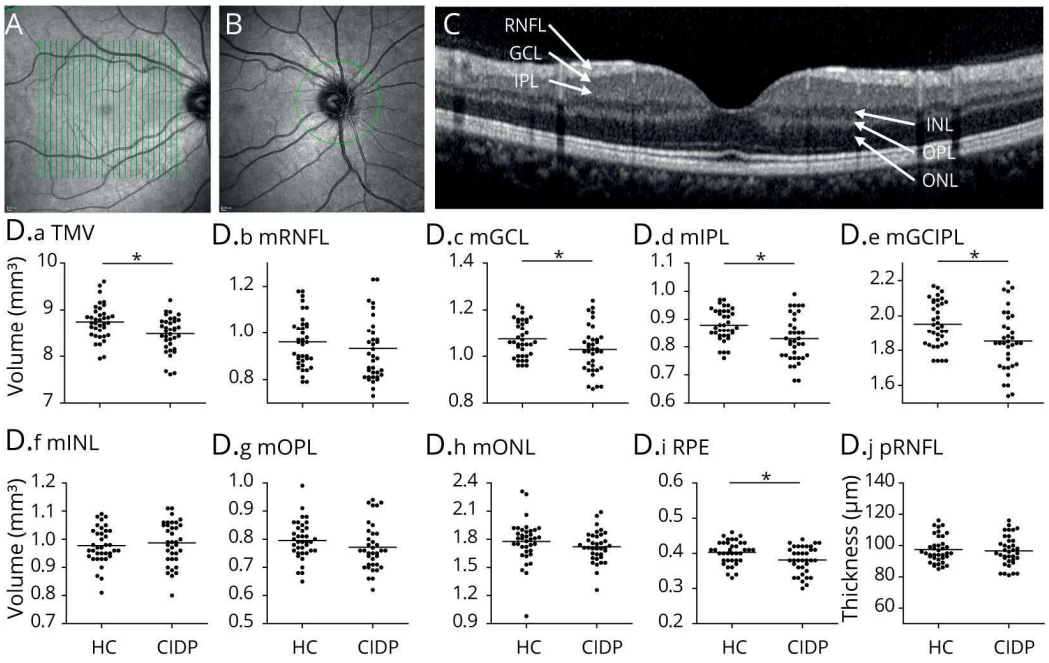
In an exploratory approach, we correlated the significantly altered retinal layers (TMV, GCIPL, and pigment epithelium) with neurographical and clinical parameters in the CIDP group. We found a positive association of the motor nerve conduction velocity of the right ulnar nerve with the GCL (p = 0.02, B = 0.002, Figure 3A) and negative associations of the compound muscle action potential with the retinal pigment epithelium (RPE, p = 0.009, B = −0.003, Figure 3B) and of the sensory nerve conduction velocity with the TMV (p = 0.009, B = −0.01, Figure 3C). Regarding clinical parameters, positive

Figure 1 Flowchart of Subject Recruitment



Patients with CIDP and healthy controls were recruited at the Department of Neurology, Heinrich-Heine-University in Düsseldorf, Germany. Of the 66 individuals, 44 were patients with CIDP and 22 healthy control subjects. Of the 44 patients with CIDP who were screened, 22 individuals were excluded because of concomitant diabetes mellitus and ophthalmic pathologies. Additional 7 single eyes were excluded because of drusen and macular edema. Of the remaining individuals, 22 were patients with CIDP and 22 age- and sex-matched controls. CIDP = chronic inflammatory demyelinating polyneuropathy.

Figure 2 OCT Measurements



(A) The macular thickness and volume were calculated from consecutive vertical scans centered on the macula. (B) The peripapillary RNFL was evaluated in a circular scan centered on the optic disk. (C) The deeper retinal layers were semiautomatically segmented in a single horizontal foveal scan. The volumes of the retinal layers were assessed by averaging 14 images from vertical scans. (D) Scatter plots display the macular layer volumes or thickness. All values are described as mean ± SD. Each point represents 1 eye. The mean of all eyes is represented by the horizontal line. Statistical differences in patients with CIDP vs healthy controls were assessed by GEE accounting for several measurements in the same individual (2 eyes). GEE = generalized estimation equation; mGCIPL = macular ganglion cell/inner plexiform layer; mGCL = macular ganglion cell layer; mINL = macular inner nuclear layer; mIPL = macular inner plexiform layer; mONL = macular outer nuclear layer; mOPL = macular outer plexiform layer; mRNFL = macular retinal nerve fiber layer; OCT = optical coherence tomography; pRNFL = peripapillary retinal nerve fiber layer; RPE = retinal pigment epithelium; TMV = total macular volume.

associations were detected regarding the time since clinical disease manifestation and the TMV (p = 0.005, B = 0.003, Figure 3D) and the IPL (p = 0.015, B = 0.001, Figure 3E). No associations were observed between retinal layers that were found to be changed in CIDP and low-contrast visual acuity, clinical severity of the disease as assessed by ODSS, time since diagnosis, therapy duration, and CSF protein levels.

Discussion

We herein present data demonstrating subtle retinal degeneration in patients with CIDP detected by optical coherence tomography. Our observations provide further evidence for a CNS involvement in CIDP. A number of case reports or small series have implicated some connection between autoimmune peripheral demyelination and specific CNS pathologies. Two case-control studies have recently been published. We looked at mfVEPs in CIDP and found no clear-cut evidence of CIDP-dependent alterations.[14] Dziadkowski et al.[15] compared multimodal evoked potentials in patients with CIDP and HCs and detected prolonged latencies in VEP, brainstem acoustic evoked potentials, and somatosensory-evoked potentials.

Because CIDP is an autoimmune and primary demyelinating PNS disease, its most obvious CNS counterpart is MS. Classic OCT alteration in MS occurs in the pRNFL, which is decreased in thickness especially after optic neuritis,[30] but also independent of optic neuritis.[31] Here, we did not observe any alterations in pRNFL thickness in CIDP. GCIPL, which contains the neurons forming nonmyelinated axons of the RNFL and their dendritic arbors, has been shown to be also affected in patients with MS and displayed robust differences between patient and control eyes.[32,33] It has been suggested to be equivalent to the pRNFL, concerning its utility in diagnosis, monitoring, and research in MS.[16] In the GCIPL, as well as the GCL and the IPL separately, we observed a significant volume reduction in CIDP compared with HC eyes. The GCL is believed to be a sensitive biomarker of neurodegeneration[34] and may even have advantages compared with the RNFL because it is not inflicted by edema in optic neuritis in MS, and therefore, atrophy becomes detectable earlier.[35,36] In addition, GCL seems to reflect MRI changes in MS better than pRNFL, and it seems to have a lower variability in cross-sectional data.[37-39] Whether these findings are applicable in the context of CIDP, however, is unclear because we have previously found that mfVEP was not markedly altered in patients with CIDP.[14] Because mfVEP is quite sensitive in detecting optic nerve damage, the significant changes in the GCL may therefore point toward a retinal, rather than optic nerve pathology. Another explanation may be a degenerative process in the posterior visual pathway, which could lead to

Table Demographical, Clinical, and OCT Parameters of Patients With CIDP and HCs

Characteristics	Patients with CIDP n = 22	HCs n = 22	*p* Value
Age (y, mean ± SD)	58.27 ± 12.91	57.68 ± 12.21	—
Male	14 of 22 (63.6%)	13 of 22 (59.1%)	—
White ethnicity	22 of 22 (100%)	21 of 22 (95.5%)	—
Disease duration at OCT (mo, mean ± SD)	102.5 ± 81.9	n.a.	—
Duration of IVIG treatment at OCT (mo, mean ± SD)	41.40 ± 36.48	n.a.	—
ODSS at OCT (mean ± SD)	3.11 ± 1.69	n.a.	—
OCT parameters			
TMV (mm^3, mean ± SD)	8.48 ± 0.38 (−3.1%)	8.75 ± 0.37	0.018
mRNFL volume (mm^3, mean ± SD)	0.93 ± 0.15	0.96 ± 0.11	0.415
GCIPL volume (mm^3, mean ± SD)	1.86 ± 0.17 (−4.6%)	1.95 ± 0.13	0.018
GCL volume (mm^3, mean ± SD)	1.03 ± 0.10 (−3.7%)	1.07 ± 0.11	0.037
IPL volume (mm^3, mean ± SD)	0.83 ± 0.08 (−5.6%)	0.88 ± 0.06	0.015
INL volume (mm^3, mean ± SD)	0.99 ± 0.08	0.98 ± 0.06	0.715
OPL volume (mm^3, mean ± SD)	0.77 ± 0.08	0.80 ± 0.07	0.067
ONL volume (mm^3, mean ± SD)	1.72 ± 0.16	1.78 ± 0.23	0.758
Pigment epithelium volume (mm^3, mean ± SD)	0.38 ± 0.04 (−5.0%)	0.40 ± 0.03	0.020
pRNFL thickness (μm, mean ± SD)	96.58 ± 9.55	97.37 ± 8.39	0.635

Abbreviations: CIDP = chronic inflammatory demyelinating polyneuropathy; IVIG = IV immunoglobulins; mGCIPL = macular ganglion cell/inner plexiform layer; mGCL = macular ganglion cell layer; mINL = macular inner nuclear layer; mIPL = macular inner plexiform layer; mRNFL = macular retinal nerve fiber layer; mONL = macular outer nuclear layer; mOPL = macular outer plexiform layer; n.a. = not available; OCT = optical coherence tomography; ODSS = overall disability sum score; pRNFL = peripapillary retinal nerve fiber layer.
Indicated are the demographical, clinical, and optical coherence tomography parameters as means and SD.

retrograde transsynaptic degeneration in the retina. However, the lack of MRI brain imaging limits this study in assessing for that possibility.

We also noted a decrease in RPE layer volumes in patients with CIDP. Concerning embryology, the RPE stems from neuroectodermal cells, and thus, these epithelial cells can be considered as CNS cells.[40] The biological context of this finding seems unclear. The TMV was significantly decreased in patients with CIDP, which rather reflects a thinning of single retinal layers.

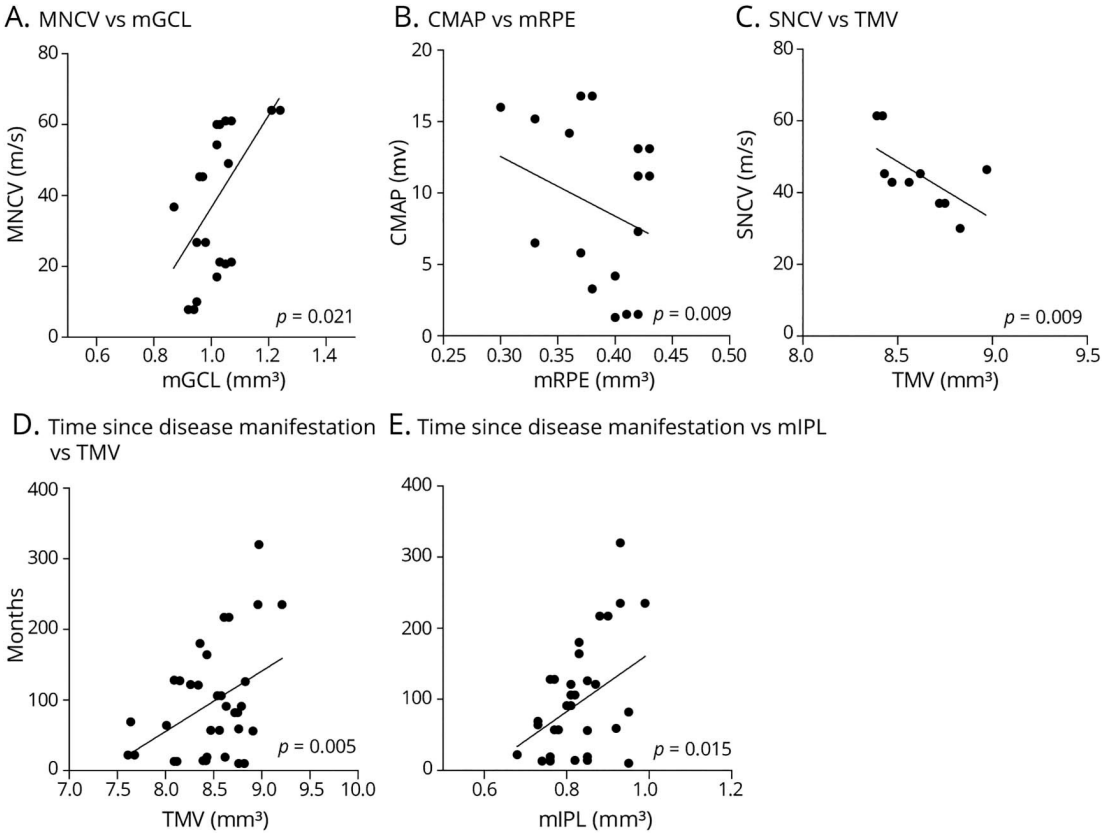
At this point, it can only be speculated how retinal degeneration and immune mediated peripheral nerve damage are linked biologically. Retinal atrophy can result from retrograde degeneration after an insult to the optic nerve, activation of apoptotic pathways, and glial activation.[41-44] Because CIDP is an autoimmune disease, one possibility would be the presence of a common antigen in peripheral nerves and the optic nerve or the retina, but to date, none has been identified.

A direct immune attack on the retina remains a theoretical possibility, but likewise, nothing is known about antigens shared with peripheral nerves. To learn more about possible clinical implications, we investigated relations between the retinal layer volumes and nerve conduction and clinical parameters. In an exploratory approach, we found a number of associations. The most remarkable was a positive association between the macular GCL volume and the motor nerve conduction velocity of the right ulnar nerve.

The study has obvious limitations. The cohort size of 22 individuals per group does allow for statistical evaluation, but it does not withstand corrections for multiple testing. Because the study is explicitly of exploratory nature, we deem this to be acceptable. Furthermore, our findings suggest that an in-depth investigation of the visual pathway is warranted in CIDP by, for example, applying OCT side-by-side with MRI covering the optic radiation. Although this was not part of the current investigation, it would be important and of interest to correlate subclinical MRI involvement with OCT alterations in CIDP.

Taken together, the data suggest degenerative processes in the retina and thus the CNS in CIDP. Particularly, the changes in the GCIPL could point to underlying processes that may be

Figure 3 Analysis of Associations With Neurographic and Clinical Features



Scatter plots of associations of retinal layers with nerve conduction and compound action potential amplitudes of the right ulnar nerve, as well as time since disease manifestation in patients with CIDP vs. healthy controls. Each dot represents 1 eye, *p* values (GEE method), and regression lines are provided. (A) Positive association of MNCV with mGCL ($p = 0.021$). (B) Negative association of CMAP with mRPE ($p = 0.009$). (C) Negative association of SNCV with TMV ($p = 0.009$). (D and E) Positive association of the time of OCT measurement since disease manifestation with TMV (D, $p = 0.005$) and mIPL (E, $p = 0.015$). CIDP = chronic inflammatory demyelinating polyneuropathy; CMAP = compound motor action potential; GEE = generalized estimation equation; mGCL, macular ganglion cell layer; mIPL, macular inner plexiform layer; MNCV, motor nerve conduction velocity; mRPE, macular retinal pigment epithelium; SNCV, sensory nerve conduction velocity; TMV, total macular volume.

functionally and biologically relevant. To consolidate these intriguing findings, an independent longitudinal study of a larger patient cohort should be conducted.

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Disclosure

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Jonas Graf, MD	Department of Neurology, Medical Faculty, Heinrich-Heine-University Düsseldorf, Germany	Drafting/revision of the article for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
Julia Kluge	Department of Neurology, Medical Faculty, Heinrich-Heine-University Düsseldorf, Germany	Major role in the acquisition of data; Analysis or interpretation of data
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RESEARCH ARTICLE

Multifocal visual evoked potentials in chronic inflammatory demyelinating polyneuropathy

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Abstract

Objective: Studies using conventional full-field visual evoked potentials (ffVEP) have reported subtle abnormalities in patients with chronic inflammatory demyelinating polyneuropathy (CIDP). We hypothesize that these abnormalities can be detected in the majority of CIDP patients using enhanced methods. **Methods:** We performed a cross-sectional noninterventional study comparing 18 CIDP patients and 18 matched healthy controls using multifocal VEP (mfVEP) as a technique with enhanced sensitivity to detect conduction abnormalities across the spectrum of optic nerve fibers. Patients with confounding diseases (ophthalmologic, diabetes mellitus) were excluded. **Results:** The mean amplitude and latency, as well as the low-contrast visual acuity, did not differ between CIDP patients and controls. Subanalyses revealed latency differences concerning the superior sector of the visual field. Severity markers of CIDP (ODSS, motor nerve conduction velocity) were associated with mfVEP latency delay. **Interpretation:** We could not adduce evidence for clinically or diagnostically relevant visual pathway involvement in CIDP. The latency differences identified were very subtle and restricted to the superior visual field which cannot be readily explained biologically, anatomically, or pathologically. In summary, we conclude that our study revealed no relevant differences in mfVEP parameters between CIDP patients and controls.

Introduction

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a subacute or chronic autoimmune neuropathy pathologically characterized by demyelination and secondary axonal degeneration of peripheral nerves.[1,2] Interestingly, previous studies suggested that central nervous system (CNS) involvement, including the visual pathway, may also occur in this disease.[3–5] Of note, subclinical CNS involvement in CIDP patients, that is, pathological ffVEP measurements have been described before.[3] Hawke et al.[6] reported abnormal magnetic resonance imaging (MRI) characterized by high white matter signals in six out of 26 cases. Furthermore, 14 out of 28 cases were reported by Ormerod et al.[7] Thomas et al.[8] described a series of six cases in which a chronic demyelinating neuropathy was associated with a relapsing multifocal demyelinating CNS disorder: five of six cases showed prolonged full-field visual evoked potentials (ffVEP) latencies in one or both eyes along with T2 signals on cranial MRI. These authors reviewing pathological reports and studies on experimental models raised the issue of shared pathogenic mechanisms explaining involvement of both the peripheral and central nervous system. In a recent nationwide study of combined central and peripheral demyelination (CCPD) in Japan, 15 out of 21 cases showed ffVEP abnormalities,[9] whereas a CCPD study in China revealed pathological ffVEPs in 11 out of 22 patients.[10] The pathophysiological mechanism underlying CNS involvement is not understood. It has been suggested that the CNS and PNS may share antigens to which aberrant humoral or T-cell immune responses are directed. This

has been hypothesized for circulating M-proteins[3] in monoclonal gammopathy-associated peripheral neuropathies with CNS involvement and in combined central and peripheral demyelination in Japan where Neurofascin-155 was reported to represent a shared antigen recognized by antibodies circulating in the blood of CIDP patients.[9] In the largest conducted clinicopathological study on 100 French patients with CIDP, five patients presented with symptomatic CNS involvement.[11]

Of note, in the previous studies using conventional full-field visual evoked potentials (ffVEP), CIDP patients were not compared with age- and sex-matched controls and confounding ophthalmic and systemic disorders that may be relevant in these cohorts of predominantly elderly patients have not been accounted for. Therefore, we performed a cross-sectional, noninterventional study of CIDP patients and age- and sex-matched healthy controls without confounding concomitant diseases such as ophthalmic pathologies and diabetes mellitus by measuring multifocal visual evoked potentials (mfVEPs). This technique is able to detect visual pathway abnormalities with substantially enhanced sensitivity by recording simultaneously from multiple regions of the visual field.[12]

The primary aim of our study was to investigate the hypothesis that mfVEP, due to its sensitivity, may be suitable to detect visual system pathology even in CIDP patients without clinically overt visual dysfunction or other signs of CNS involvement.

Methods

Patients

Patients were prospectively recruited at the Department of Neurology, Heinrich-Heine-University in Düsseldorf, Germany. Inclusion criteria were age >18 years, probable or definite CIDP according to the EFNS/PNS CIDP Guidelines[13] and response to immunomodulatory treatment. Out of 61 subjects (43 CIDP patients, 18 healthy controls), a total of 25 CIDP patients and seven eyes were excluded: nine patients and seven eyes due to ophthalmic pathologies (one glaucoma, two cataract, four bilateral drusen, one papilledema, one choroidal neovascularization, one eye with macular edema, six eyes with drusen), 13 patients because of diabetes mellitus,[14] two patients due to head tremor interfering with the mfVEP assessment and one patient who was positive for anti-MAG-IgM. The remaining 36 subjects were 18 patients with CIDP and 18 age- and sex-matched healthy controls (Fig. 1). Three CIDP patients had a monoclonal gammopathy. INCAT ODSS[15] (Inflammatory Neuropathy Cause and Treatment, Overall Disability Sum Score) was assessed in all CIDP patients. All patients and controls included in the final analysis showed no abnormalities on neuroophthalmological examination including assessment of corrected visual acuity (Sloan charts), tonometry, slit lamp examination, fundoscopy, and optical coherence tomography. In addition, all patients and controls were tested for corrected low-contrast letter recognition using 2.5% low-contrast early treatment of diabetic retinopathy (ETDRS) charts. As nerve conduction studies of the lower limbs and sensory nerve conduction studies of the upper limbs showed a high rate of signal loss, motor nerve conduction velocity (MNCV) of the right ulnar nerve was used to investigate the association with mfVEP parameters.

Matched controls did not have any symptoms suspicious of polyneuropathy. An overview of the patient and healthy control cohorts is provided in Tables S1 and S2.

Multifocal visual evoked potentials

Multifocal visual evoked potentials (mfVEPs) were measured as described previously[16]: The Visionsearch® mfVEP device applies simultaneous multifocal stimulation of 56 segments of the visual field (24° of eccentricity) via a 68 sec pseudorandom sequence and recording a 2-channel visual response using a custom designed occipital cross electrode holder which predetermines the four occipital electrode positions.[17] Cross-correlation of the event-related response with the sequence itself allows for recording of evoked potentials in the nanovolt range, which originate from monocular stimulation of distinct areas of the visual field.

The 56 segments of the visual field can be assigned either to four sectors (Fig. S1A) or to five eccentricities (Fig. S1B). Regarding the sectoral division, 18 segments each belong to the superior (segments: 6–7, 16–19, 28–31, 40–43, 52–55) and inferior sector (segments: 2–3, 10–13, 22–25, 34–37, 46–49), whereas the temporal (segments: 1, 8–9, 20–21, 32–33, 44–45, 56) and nasal sector (segments: 4–5, 14–15, 26–27, 38–39, 50–51) consist of 10 segments each. Concerning the eccentricities, segments can be arranged in circles. The central circle comprises eight segments (segments: 1–8), while the peripheral circles consist of 12 segments each.

Statistical evaluation

Statistical analyses were performed using SPSS Statistics 24 (IBM). Generalized estimation equation models (GEE) accounting for within-subject intereye or intersegment correlations using an exchangeable working correlation matrix and correcting for age and sex were applied to analyze associations between mfVEP parameters and clinical data and to test for differences in the mfVEP

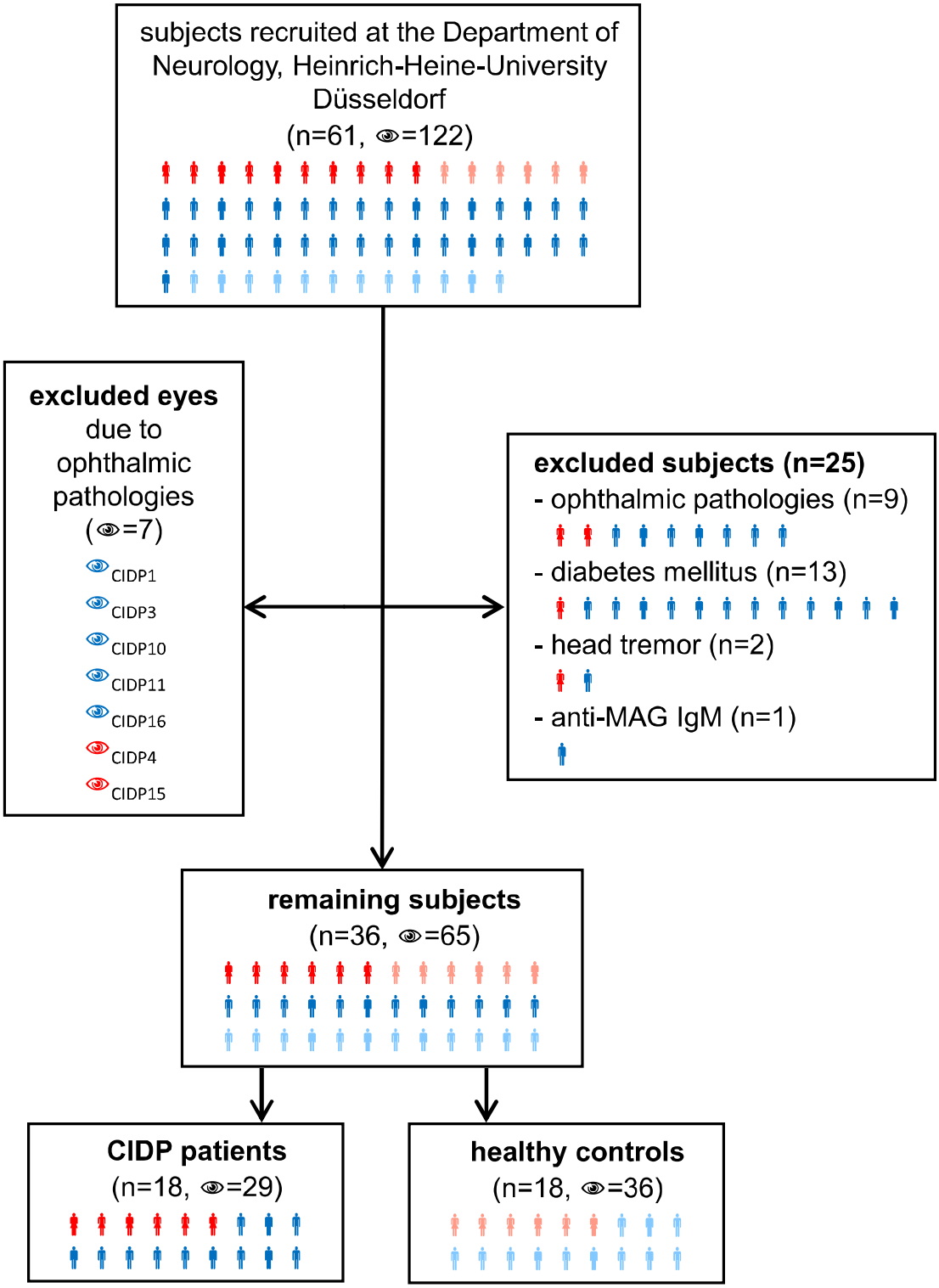

Figure 1. Recruitment. Flowchart of the subject recruitment at the Department of Neurology, Heinrich-Heine-University Düsseldorf. Twenty-five of the 61 subjects were excluded: nine due to ophthalmic pathologies, 13 due to diabetes mellitus, two due to head tremor, and one due to positive anti-MAG-IgM. Seven of the 122 eyes were excluded due to ophthalmic pathologies. The remaining 36 subjects were composed of 18 healthy volunteers (36 eyes) and 18 CIDP patients (29 eyes). Red symbols represent female CIDP patients, blue symbols, male CIDP patients. Female healthy volunteers are shown in light red and male healthy volunteers in light blue.

Table 1. mfVEP parameter overview of CIDP patients and healthy controls regarding the different sectors and eccentricities (STD = standard deviation, CIDP = chronic inflammatory demyelinating polyneuropathy, HC = healthy controls, Eccentr. = eccentricity, 1st per. = first peripheral, 2nd per. = second peripheral, 3rd per. = third peripheral, 4th per. = outer peripheral).

			Latency (msec)			Amplitude (nV)		
Group			Mean	STD	Range	Mean	STD	Range
CIDP	Sector	Superior	156.16	18.29	111.70–253.30	146.14	57.96	43.90–343.40
		Inferior	144.45	15.93	116.70–236.70	214.21	77.49	57.60–500.00
		Temporal	148.13	21.36	106.70–243.30	173.41	68.66	45.40–459.90
		Nasal	148.83	15.57	120.00–231.70	197.50	74.70	63.50–459.40
	Eccentr.	Central	151.36	20.10	111.70–230.00	175.97	85.27	45.40–459.90
		1st per.	151.01	17.13	106.70–243.30	186.84	79.51	58.50–500.00
		2nd per.	148.43	15.73	120.00–235.00	192.48	67.81	61.3–396.40
		3rd per.	149.13	17.91	118.30–253.30	179.70	71.16	47.10–411.10
		4th per.	148.90	20.86	116.70–243.30	173.28	72.98	43.90–418.80
HC	Sector	Superior	151.29	19.72	115.00–266.70	147.73	46.72	54.20–334.70
		Inferior	142.96	16.88	113.30–243.30	220.33	85.31	76.80–608.20
		Temporal	148.12	19.58	106.70–266.70	171.50	59.93	47.10–394.10
		Nasal	150.10	17.99	120.00–266.70	193.77	69.41	52.20–432.30
	Eccentr.	Central	147.67	18.74	106.7–248.3	184.11	71.86	52.20–470.20
		1st per.	147.57	16.62	116.70–266.70	192.45	73.41	50.80–493.10
		2nd per.	147.78	17.87	118.30–266.70	195.77	76.61	47.10–550.80
		3rd. per.	147.28	18.87	113.30–263.30	176.90	70.66	53.20–594.10
		4th per.	148.83	21.71	116.70–266.70	168.61	72.04	54.20–608.20

parameters between CIDP patients and controls. Adjusted *P*-values (adj. *P*) were calculated using Bonferroni correction in the case of multiple group analyses. Statistical power analyses were operated using G*Power 3.1.9.2. An online calculator by Psychometrica was utilized to calculate effect size, Cohen's d (d_{Cohen}) and the associated confidence intervals.

Ethics

The local ethics committee of Heinrich-Heine-University Düsseldorf approved this study (registry number 4849). Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki.

Results

Primary hypothesis – difference in mean amplitude and mean latency

In patients with CIDP, mfVEP revealed a mean amplitude of 182.06 ± 48.37 nV (range = 94.55–268.98 nV) and a mean latency (first peak) of 149.65 ± 6.51 msec (range = 137.88–161.78 msec). In healthy controls, the examination revealed a mean amplitude of 183.53 ± 43.85 nV (range = 101.94–276.79 nV) and a mean latency (first peak) of 147.84 ± 5.68 msec (range = 137.65–164.11 msec). There was no single patient with pathological mean, sector or eccentricity latencies or amplitudes compared to our age- and sex-matched controls. An overview is provided in Table 1. There was no statistical difference in mean amplitude ($P = 0.855$, mean difference = 1.47 ± 11.46 nV (95%-CI = [−24.36–21.42]), Fig. 2A) or first peak latency ($P = 0.213$, mean difference = 1.81 ± 1.51 msec (95%-CI = [−1.21–4.84]), Fig. 2B) between both groups.

Due to the rather small sample size we cannot exclude subtle differences between CIDP patients and controls. Therefore, we performed a power analysis to determine the sample size needed to detect possible significant differences based on our data. Our results for the amplitude difference reached an effect size of 0.022 (power = 0.05, $d_{Cohen} = 0.032$ (95%-CI = [−0.46–0.52]) and for the latency difference an effect size of 0.36 (power = 0.30, $d_{Cohen} = 0.30$ (95%-CI: [−0.19–0.79]), This suggests that 121 and 32,598 patients would be needed to reach a power ($1-\beta$) of 0.8 for latencies and amplitudes, respectively.

Secondary outcomes – subanalyses

First, we created heatmap-graphics for amplitude (Fig. 3A) and latency (Fig. 3B) showing the differences in each segment of the visual field between CIDP patients and healthy controls. These were calculated using the following formula:

$$\text{difference} = \text{value CIDP} - \text{value healthy control}$$

Second, we performed systematical analyses regarding the different sectors and eccentricities. The statistical

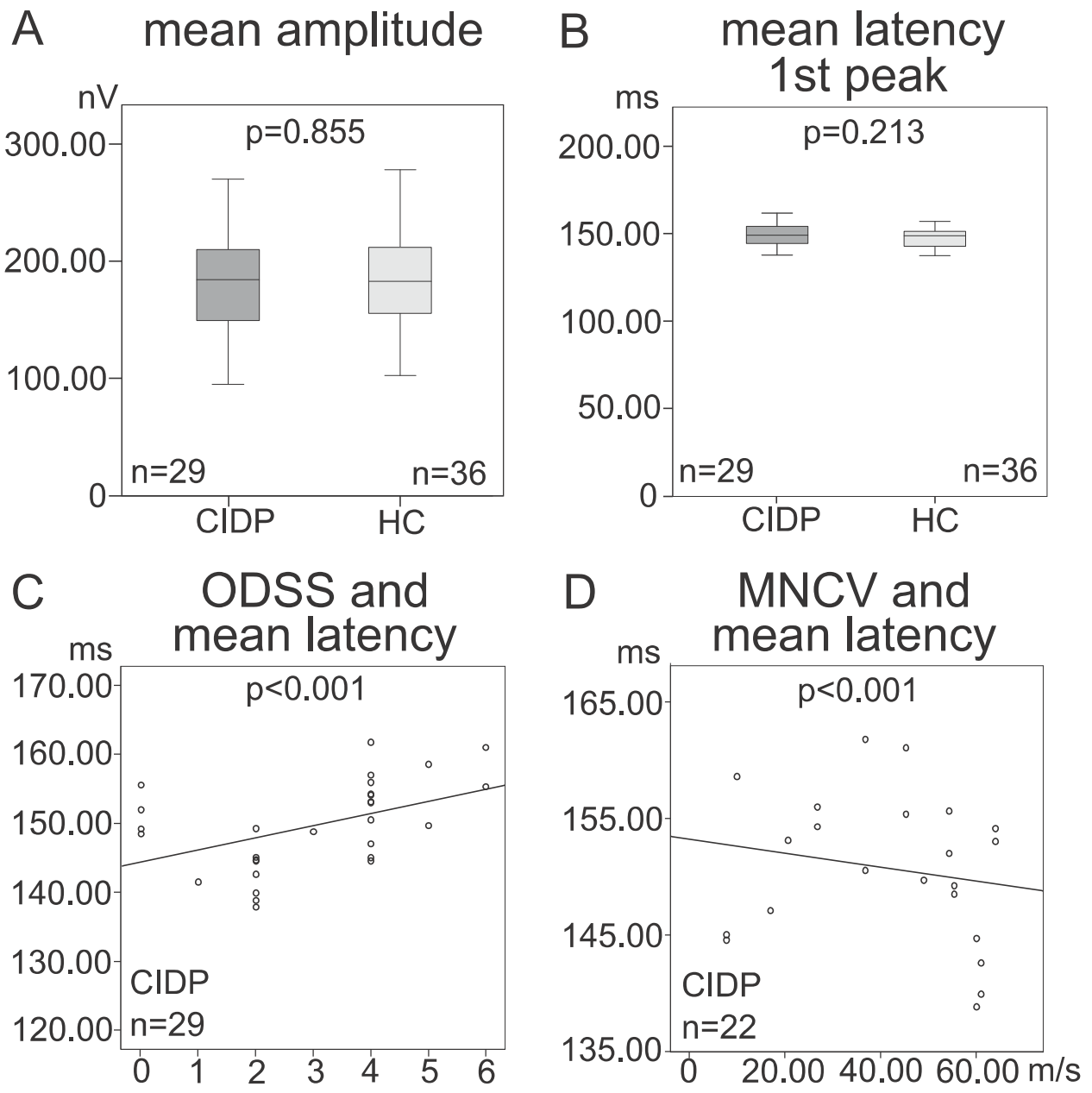

Figure 2. mfVEP parameters of CIDP patients and healthy controls (HC). Box-and-whisker plots of the mean amplitude in nV (A) and the mean latency of the first peak in msec (B). The black line within the box indicates the mean, the box marks the interquartile range and the whiskers represent the minimum and maximum. Scatter plots of the association between the ODSS (overall disability sum score) and the mean latency (C), and the MNCV (motor nerve conduction velocity) of the right ulnar nerve in m/sec and the mean latency (D). Each eye is shown as a dot. Regression lines, numbers of eyes, and *P* -values (GEE analysis) are provided for the different mfVEP parameters.

analysis of the sectors showed significant difference in first peak latency concerning the superior sector ($P = 0.005$, adj. $P = 0.015$, Fig. S2A) between both groups. There was no statistical difference regarding the remaining parameters. An overview of the results is provided in Table 2.

To examine if the severity of CIDP relates to mfVEP parameters, we performed analyses concerning ODSS and the motor nerve conduction velocity (MNCV, Table 2).

The ODSS in CIDP patients ranged from 0 to 6 (median = 4, mean = 3.11 ± 1.69). There was no significant association of amplitude with ODSS ($P = 0.296$, $B = 6.129$),

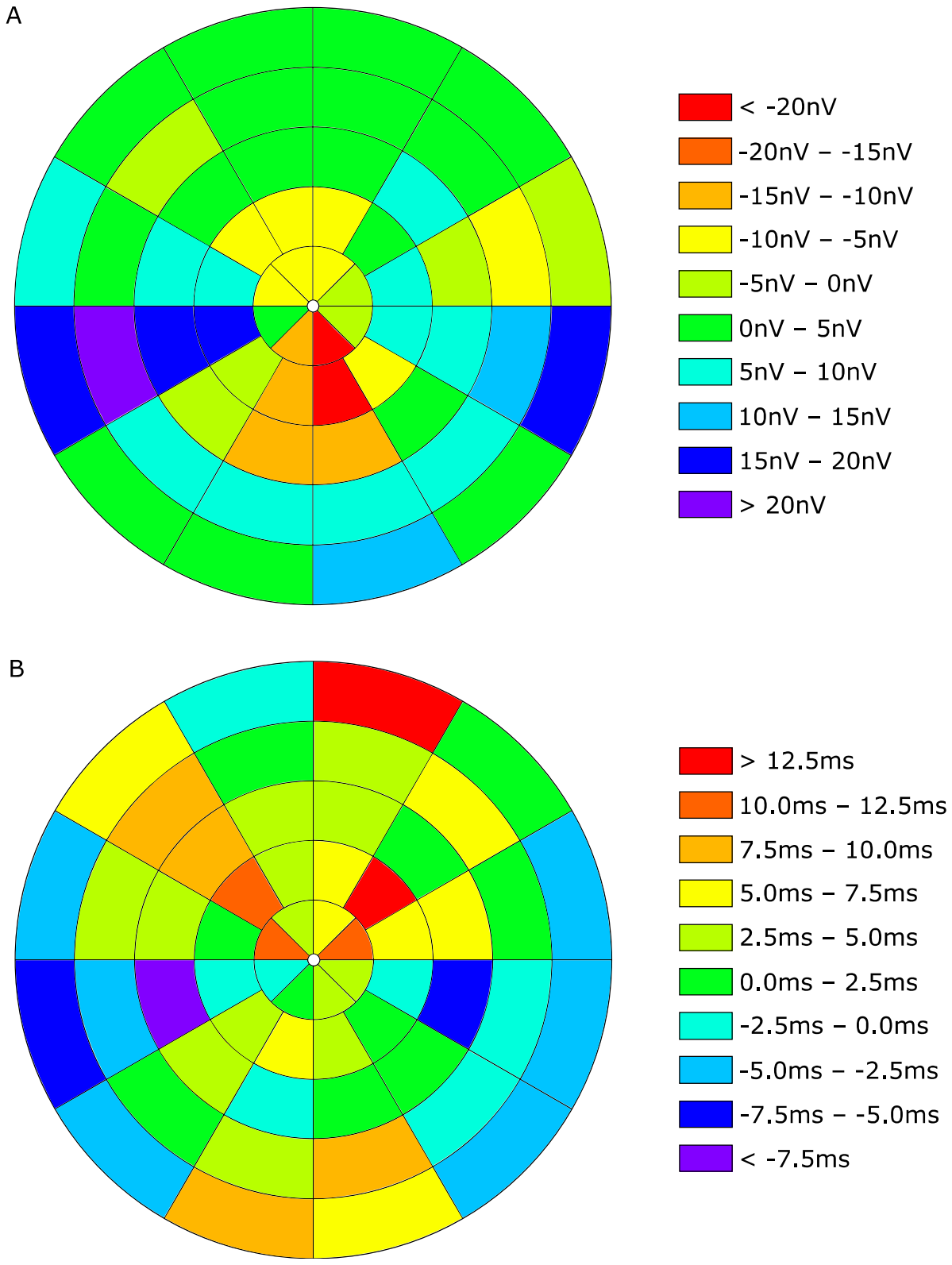

Figure 3. Differences in each segment of the visual field between CIDP patients and healthy controls (HC). Heat maps show the amplitude in nV (A) and the latency in msec (B). Different colors represent the positive or negative value of the differences (CIDP – HC).

Table 2. Overview of secondary outcome subanalyses. Table showing association analyses of the mean mfVEP parameters with the ODSS and MNCV, as well as analyses regarding the sectors and eccentricities (GEE analysis).

			Latency			Amplitude		
Primary measure	Secondary measure	Tertiary measure	*P*	adj. *P*	*B*	*P*	adj. *P*	*B*
Mean	ODSS ass.		**<0.001**		**1.318**	0.296		6.129
	MNCV ass.		**<0.001**		**−0.081**	0.738		−0.170
Sector	Superior		**0.005**	**0.015**	**5.205**	0.684	n.s.	−4.266
	Inferior		0.226	n.s.	1.712	0.782	n.s.	−5.271
	Temporal		0.896	n.s.	0.313	0.940	n.s.	1.112
	Nasal		0.531	n.s.	−1.483	0.781	n.s.	4.630
	Superior	MNCV ass.	0.418	n.s.	−0.039	0.188	n.s.	−0.567
	Inferior	MNCV ass.	0.092	n.s.	−0.073	0.995	n.s.	0.004
	Temporal	MNCV ass.	**0.006**	**0.018**	**−0.160**	0.830	n.s.	0.123
	Nasal	MNCV ass.	0.084	n.s.	−0.096	0.849	n.s.	−0.129
Eccentricity	Central		0.173	n.s.	3.622	0.723	n.s.	−6.896
	First peripheral		0.104	n.s.	3.626	0.787	n.s.	−4.960
	Second peripheral		0.679	n.s.	0.811	0.791	n.s.	−4.212
	Third peripheral		0.224	n.s.	2.081	0.916	n.s.	1.369
	Outer peripheral		0.917	n.s.	0.168	0.754	n.s.	3.867
	Central	MNCV ass.	0.659	n.s.	−0.027	0.589	n.s.	−0.419
	First peripheral	MNCV ass.	**0.003**	**0.012**	**−0.119**	0.807	n.s.	−0.166
	Second peripheral	MNCV ass.	0.085	n.s.	−0.079	0.951	n.s.	−0.031
	Third peripheral	MNCV ass.	**0.011**	**0.044**	**−0.100**	0.796	n.s.	−0.136
	Outer peripheral	MNCV ass.	0.293	n.s.	−0.049	0.608	n.s.	−0.272

Bonferroni Correction was used for adjusted *P*-values. Significant results are highlighted in bold and light gray. (*P* = *P*-value, adj. *P* = adjusted *P* -value, n.s. = not significant, ass. = association, MNCV = motor nerve conduction velocity, ODSS = overall disability sum score).

but a significant positive association between first peak latency and ODSS ($P < 0.001$, $B = 1.318$, Fig. 2C).

MNCV of the right ulnar nerve was used for analysis. CIDP patients showed a mean MNCV of 39.08 ± 19.96 m/sec (range: 7.80–64.00 m/sec). There was no significant association between MNCV and amplitude ($P = 0.738$, $B = -0.170$), but a significant negative association between MNCV and mfVEP latency ($P < 0.001$, $B = -0.081$, Fig. 2D). Therefore, we performed subanalyses regarding sectors and eccentricities. Temporal sector ($P = 0.006$, adj. $P = 0.018$, $B = -0.160$, Fig. S2B), first peripheral eccentricity ($P = 0.003$, adj. $P = 0.012$, $B = -0.119$, Fig. S2C), and third peripheral eccentricity ($P = 0.011$, adj. $P = 0.044$, $B = -0.100$, Fig. S2D) showed significant negative associations, but none of the other parameters (Table 2).

Furthermore, we performed an analysis of the 2.5% low-contrast visual acuity (LCV) between both groups and an association analysis of the LCV versus the mfVEP parameters.

In CIDP patients, there was a mean LCV of 0.33 ± 0.15 (range: 0.05–0.60) and in healthy controls 0.36 ± 0.11 (range: 0.12–0.63), the analysis revealed no significant difference between both groups ($P = 0.500$). CIDP patients showed a significant association of LCV with amplitude ($P = 0.040$, $B = 108.549$, Fig. S2E), but not between LCV and latency ($P = 0.111$, $B = -8.219$). In healthy controls, neither amplitude ($P = 0.607$, $B = -20.136$, Fig. S2E), nor latency ($P = 0.102$, $B = -10.132$) revealed significant associations with LCV.

Discussion

Certain inflammatory neuropathies like Miller Fisher syndrome and Bickerstaff brainstem encephalitis are associated with involvement of cranial nerves and the central nervous system, respectively.[18,19] In classic CIDP, clinical symptoms are usually restricted to the peripheral nervous system. Identifying CNS involvement in CIDP, which might be detectable by sensitive methods, would be of interest, for example, to evaluate progression in severe cases where peripheral nerve conduction studies are sometimes challenging due to a lack of action potentials. In contrast to previous studies[3–5] that used traditional ffVEP, we found no difference of mean mfVEP amplitudes or latencies in our cohort of patients without clinical signs of CNS involvement compared to matched controls. Therefore, our primary hypothesis of altered mean mfVEP latencies or amplitudes has to be refuted.

In an exploratory subanalysis, we found a significant delay in latencies in the superior sector of the visual field and associations of mfVEP measures with the clinical

ODSS and the mean MNCV of our CIDP patients. However, since there is no simple biological, anatomical, or pathological explanation for these results; these exploratory findings need to be interpreted with great caution and we cannot rule out a false-positive result despite the Bonferroni correction for multiple testing. Of note, if the Bonferroni correction is performed for the total number of tests performed, instead of only correcting for the number of subanalyses, the difference in latency of the superior sector loses significance. The fact that we observed a significant association of mean mfVEP latency with ODSS and MNCV is surprising considering that mean latency did not differ between patients and controls. Possible explanations are CIDP-independent effects, for example, metabolic factors influencing both mfVEP latency and MNCV/CIDP severity, and/or a subtle involvement of the visual system only in severe cases of CIDP with ODSS above 4. Larger studies on severely affected CIDP patients including MNCV assessments also in healthy controls would be needed to address these points. However, we have to acknowledge, that the association remains weak and therefore a clinical relevance cannot be postulated.

Therefore, considering all these caveats, the significant differences observed are unlikely to be meaningful in a clinical setting.

We conclude that despite carefully selecting the patient cohort and using both enhanced mfVEP techniques, adequate inclusion and exclusion criteria and suitable statistical methods for visual outcome measures to account for intereye within-patient dependencies[20] a clinically relevant visual pathway involvement in CIDP cannot be elicited. Reasons for the positive results of the previous studies using full-field VEPs[3–5] remain subject to discussion. Possible explanations include the lack of age- and sex-matched controls and differences in the composition the cohorts studied, for example, including also patients with signs of CNS involvement, or patients with other peripheral neuropathies, for example, hereditary neuropathy with pressure palsies (HNPP) and Charcot–Marie–Tooth disease type 1A (CMT1A).[1] Further well-controlled longitudinal studies involving larger cohorts of different disease entities and higher numbers of severely affected patients are warranted to refute or corroborate these results and investigate their relevance. All in all, considering the data presented here, mfVEPs do not seem promising as a monitoring parameter for CNS involvement in CIDP in the clinical routine.

Author Contributions

Jonas Graf contributed to the study concept/design, acquisition/analysis/interpretation of data, and drafting of the manuscript. Lea Kristina Jansen contributed to the study concept/design, acquisition/analysis/interpretation of data. Jens Ingwersen contributed to the acquisition/analysis/interpretation of data, critical revision of the manuscript. Marius Ringelstein contributed to the analysis/interpretation of data, critical revision of the manuscript. Alexander Klistorner contributed to the analysis/interpretation of data. Jens Harmel, Jana Rybak, Laura Rhöse, and Lena Gemerzki contributed to the acquisition of data. John-Ih Lee contributed to the acquisition of data and critical revision of the manuscript. Robert Kolbe and Rainer Guthoff contributed to the analysis/interpretation of data. Hans-Peter Hartung contributed to the study concept, input, and critical revision of the manuscript. Orhan Aktas contributed to the study concept/design, critical revision of the manuscript. Philipp Albrecht contributed to the study concept/design, acquisition/analysis/interpretation of data, drafting, and revision of the manuscript.

Conflicts of Interest

Jonas Graf, Lea Kristina Jansen, Jens Ingwersen, Jens Harmel, Jana Rybak, John-Ih Lee, Laura Rhöse, Lena Gemerzki, and Robert Kolbe report no conflicts of interest. Marius Ringelstein has received consulting and speaker honoraria as well as travel reimbursements from Bayer Healthcare, Biogen, Genzyme, Teva, Merz, and Novartis. Alexander Klistorner reports grants from Biogen, and Novartis. Rainer Guthoff received speaker honoraria and travel/accommodation/meeting expenses from Novartis, Roche, and Bayer Schering. Hans-Peter Hartung received, with approval of the Rector of Heinrich-Heine-University and the CEO of University of Düsseldorf Hospital, honoraria for consulting, serving on steering committees and speaking from Biogen, Geneuro, Genzyme, Medimmune, Merck, Novartis, Opexa, Receptos/Celgene, Roche, Sanofi, and Teva. Orhan Aktas received, with approval of the Rector of Heinrich-Heine-University, grants from the German Research Foundation (DFG), the German Ministry for Education and Research (BMBF) as part of the German Competence Network Multiple Sclerosis (KKNMS; for NEMOS Nation NMO-PAT FKZ 01GI1602B), the Eugène Devic European Network (EU-FP7), honoraria and travel/accommodation/meeting expenses from Almirall, Bayer, Biogen, Medimmune, Merck Serono, Novartis, Roche, Sanofi-Genzyme, and Teva. Philipp Albrecht received grants, personal fees, and nonfinancial support from Allergan, Biogen, Ipsen, Merz Pharmaceuticals, Novartis, and Roche; personal fees and nonfinancial support from Bayer Healthcare, Merck, and Sanofi-Aventis/Genzyme, outside the submitted work.

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Supporting Information

Additional Supporting Information may be found online in the supporting information section at the end of the article.

Figure S1. Visual fields, segments, sectors, and eccentricities of each eye. Graphics represent the classification into sectors (A) and eccentricities (B). Each segment is labeled by a number (1–56). The different colors of the segments mark the related sector in (A) (superior = green, nasal = pink, inferior = dark blue, temporal = purple) and the eccentricity in (B) (central = yellow, first peripheral = orange, second peripheral = red, third peripheral = light blue, fourth peripheral = gray).

Figure S2. mfVEP parameters of CIDP patients and healthy controls (HC). Box-and-whisker plot of the latency of the superior sector in msec (A). The black line within the box marks the mean, the box shows the interquartile range and the whiskers indicate the minimum and maximum. Scatter plots of the association between the MNCV (motor nerve conduction velocity) of the right ulnar nerve in m/sec and the latency of the temporal sector (B), the first (C) and third peripheral

eccentricity (D), as well as the LCV (low-contrast visual acuity 2,5% provided in decimals) versus the mean amplitude (E). Each eye is shown as a dot. Regression lines, numbers of eyes (B–E) or visual fields (A), *P*-values (GEE analysis), and adjusted *P*-values (Bonferroni Correction) are provided for the different mfVEP parameters. LCV data were available for CIDP patients and controls. Therefore, the associations between mean amplitude and LCV are provided for both groups presenting CIDP patients in green and healthy controls in black (E).

Table S1. Detailed overview of multifocal visual evoked potential and visual acuity data in CIDP patients in Düsseldorf.

Table S2. Detailed overview of multifocal visual evoked potential and visual acuity data in healthy control subjects in Düsseldorf.

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RESEARCH ARTICLE Open Access

Meningitis gone viral: description of the echovirus wave 2013 in Germany

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Abstract

Background: Aseptic meningitis epidemics may pose various health care challenges.

Methods: We describe the German enterovirus meningitis epidemics in the university hospital centers of Düsseldorf, Cologne and Berlin between January 1st and December 31st, 2013 in order to scrutinize clinical differences from other aseptic meningitis cases.

Results: A total of 72 enterovirus (EV-positive) meningitis cases were detected in our multicenter cohort, corresponding to 5.8% of all EV-positive cases which were voluntarily reported within the National Enterovirus surveillance (EVSurv, based on investigation of patients with suspected aseptic meningitis/encephalitis and/or acute flaccid paralysis) by physicians within this period of time. Among these 72 patients, 38 (52.8%) were enterovirus positive and typed as echovirus (18 pediatric and 20 adult cases, median age 18.5 years; echovirus 18 (1), echovirus 2 (1), echovirus 30 (31), echovirus 33 (1), echovirus 9 (4)). At the same time, 45 aseptic meningitis cases in our cohort were excluded to be due to enteroviral infection (EV-negative). Three EV-negative patients were tested positive for varicella zoster virus (VZV) and 1 EV-negative patient for herpes simplex virus 2. Hospitalization was significantly longer in EV-negative cases. Cerebrospinal fluid analysis did not reveal significant differences between the two groups. After discharge, EV-meningitis resulted in significant burden of sick leave in our pediatric cohort as parents had to care for the children at home.

Conclusions: Voluntary syndromic surveillance, such as provided by the EVSurv in our study may be a valuable tool for epidemiological research. Our analyses suggest that EV-positive meningitis predominantly affects younger patients and may be associated with a rather benign clinical course, compared to EV-negative cases.

Keywords: Meningitis, Echovirus, Epidemic, Surveillance

Background

Periodic aseptic meningitis epidemics can be a challenge in patient- and health care. A large retrospective analysis of a US-American cohort revealed that in 21% of cases the etiology of aseptic meningitis remains unknown [1]. Aseptic meningitis is defined [2] by an inflammation of the leptomeninx in which the causative agent cannot be identified by cerebrospinal fluid culture [3]. Viruses are the most common causes of this disease [1, 3]. Viral meningitides are predominantly caused by enteroviruses [4], which belong to the picornaviridae consisting of species A-D. The main route of infection is fecal-oral, but infestation of the respiratory tract and a droplet infection are also possible. In previous studies, viral meningitis in adults was rather associated with herpes simplex and West Nile virus, whereas children were more likely to be tested positive for enterovirus (EV) [5]. Therefore, multiple studies have been conducted in order to better understand this phenomenon: A Danish nation-wide prospective observational study between 1st of January 2015 and 30th of June 2016 revealed an unfavorable outcome of viral meningitis in 17% of all patients [6]. According to a UK study, the infection rates of viral meningitis are mainly driven by an EV predominance of echovirus 30 [7].

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EV meningitis epidemics in Shandong (People's Republic of China, 2014 [8]) and Finland (2009 and 2010 [9]) and the clinical pattern of viral central nervous system (CNS) infections in Italy [10] have previously been characterized: EV-positive patients presented with fever, nausea and vomiting, were most likely to be children, and had no clear gender predominance.

The treatment is symptomatic, employing analgetic drugs and antipyretic therapy to control body temperature. Pleconaril has been considered as potential specific treatment for EV-associated meningitis. However, it was not approved, given its just modest efficacy and considerable side-effect and interaction profile [11, 12]. In particularly severe cases, administration of immunoglobulins may positively influence the course of the disease [13].

Cerebrospinal fluid (CSF) and clinical features of EV-positive meningitis patients in Germany [14] and the differences in adult and pediatric EV-positive meningitis patients in Switzerland [15] have already been analyzed, but there is still a paucity of data describing the differences in EV-positive meningitis and EV-negative meningitis patients.

Methods

We conducted a retrospective chart review study at the Departments of Neurology of the Heinrich-Heine University Düsseldorf, the University Hospital of Cologne, the Charité – Universitätsmedizin Berlin and the Department of General Pediatrics, Neonatology and Pediatric Cardiology of the Heinrich-Heine University Düsseldorf searching for all patients with aseptic CNS infection in 2013. The study was approved by the ethics committee, University of Düsseldorf (registry number 4423). We used ICD-10 codes to identify cases of interest. As such, priority was given to the ICD-10 keys A87 and G02 (Table 1). However, as patient data may not have been in the categories listed above due to less precise encryption despite manifest illness, a wider query was additionally performed to identify all patient data encoded as A85-A89 (Other viral encephalitis, not elsewhere classified; Unspecified viral encephalitis; Viral meningitis; Other viral infections of central nervous system, not elsewhere classified; Unspecified viral infection of central nervous system, Table 1) and G02–05 (Meningitis in other infectious and parasitic diseases classified elsewhere; Meningitis due to other and unspecified causes; Encephalitis, myelitis and encephalomyelitis; Encephalitis, myelitis and encephalomyelitis in diseases classified elsewhere, Table 1). Virological testing of CSF for enteroviruses was performed in a standardized manner by the National Reference Laboratory for Poliomyelitis and Enteroviruses at the Robert Koch Institute.

Case definition

After the above-mentioned identification of patient data, the patient records were individually evaluated to exclusively select cases of aseptic meningitis defined according to the Centers for Disease Control and Prevention (CDC) [16] as acute onset of meningeal symptoms, fever, and cerebrospinal fluid pleocytosis with bacteriologically sterile cultures.

Table 1 List of ICD-10 codes utilized to identify patients with aseptic meningitis from the clinical databases of each hospital participating in this study

ICD-10	Description
A85	Other viral encephalitis, not elsewhere classified
A86	Unspecified viral encephalitis
A87	Viral meningitis
A88	Other viral infections of central nervous system, not elsewhere classified
A89	Unspecified viral infection of central nervous system
G02	Meningitis in other infectious and parasitic diseases classified elsewhere
G03	Meningitis due to other and unspecified causes
G04	Encephalitis, myelitis and encephalomyelitis
G05	Encephalitis, myelitis and encephalomyelitis in diseases classified elsewhere

Analysis

The following criteria were investigated for further analysis: Patient age, time point of manifestation, prehospital time / duration of clinical manifestation before confirmation of aseptic meningitis by CSF analyses, results of CSF diagnostics (cell count, protein content), duration of inpatient stay, type of clinical restitution (complete restitution vs. persistence of residual symptoms), for children treated in Düsseldorf time of incapacity for work of parents. CSF cell count and protein content were measured according to the local laboratory standard (Düsseldorf: turbidimetric, benzethonium chloride method, cobas® 8000, C701, Fa. Roche Diagnostics, Mannheim for protein content, mechanized cell count, UF 1000i, Sysmex for cell count; Berlin: turbidimetric assay TPUC3, Roche/Hitachi cobas® c for protein content, Fuchs-Rosenthal method for cell count; Cologne: nephelometric assay for protein content, Fuchs-Rosenthal method for cell count).

In order to put this data in perspective, we performed a query of the German-wide database of the Robert Koch Institute (RKI; EVSurv) [17] of all EV-positive meningitis cases in 2013. Data was obtained in the context of the National Enterovirussurveillance, which is based on voluntary reporting and investigation of hospitalized patients with suspected aseptic meningitis/encephalitis and/or acute flaccid paralysis. All samples were tested at the RKI using RT-nested PCR with the primers targeting the 5′NCR gene, as previously

described [18]. All PCR products were sequenced and - based on the resulting EV species - tested with species-specific PCR assays in the VP1 region for typing as recently described [19–21].

Statistical analyses were performed as indicated using SPSS Version 20 (IBM Corp. NY, USA); non-parametric testing was performed since all investigated variables were non-normally distributed (Shapiro-Wilk-test); p values < 0.05 were considered significant. If not specified otherwise, data are provided as median (25th; 75th percentile). Furthermore, a Chi-Square-test was performed in order to compare adults with children and a Spearman's correlation was performed in order to explore predictors of hospitalization. Adjusted p-values (adj. p) were calculated using Bonferroni correction, values below 0.05 were considered significant. To enhance readability of the results section, significant values are provided in three categories: < 0.05, < 0.01, and < 0.001, respectively. Finally, a multivariate, stepwise linear regression was performed in order to extract variables of potential predictive value for the time of hospitalization.

Results

Results of the retrospective analysis in Düsseldorf, Cologne and Berlin 2013.

We identified 72 EV-positive cases (31 females, 41 males) with a median age of 15 (3.25; 32.75) years. Among these 72 patients, 38 (52.8%) were echovirus-positive (18 pediatric and 20 adult cases, median age 18.5 (5.25; 31.25) years; echovirus 18 (1), echovirus 2 (1), echovirus 30 (31), echovirus 33 (1), echovirus 9 (4)), 1 patient was enterovirus 71 (EV-A71)-positive, 1 patient was coxsackie A9-positive, 1 patient was enterovirus B-positive and the specific enterovirus species of the remaining 31 EV-positive cases remained unknown or were not further typed, as not enough CSF was available for further analysis. EV-positive meningitis cases peaked in July/August (Fig. 1). Furthermore, we identified 45 enterovirus-negative cases (16 females, 29 males, median age 36 (28; 48.5) years). Among EV-negative cases, three were related to varicella zoster infection, one to herpes simplex 2 and no virus could be identified in the other patients.

Analysis of the CSF parameters cell count (EV-positive: 81 (12; 205) cells/µl, EV negative 67 (17.5; 185.25) cells/µl, Fig. 2a) and total protein (EV-positive 0.52 (0.35; 0.68) g/l, EV-negative 0.53 (0.36, 0.78) g/l, Fig. 2b) in EV-positive and EV-negative patients revealed no significant difference (Mann-Whitney U test). 2 EV-positive and 1 EV-negative CSF samples could not be evaluated due to a blood contamination.

Analysis of the number of nights spent in hospital by the patients revealed that hospitalization was significantly longer in EV-negative (6 (3; 13) nights) than in EV-positive cases (3 (1; 5) nights, adj. $p < 0.01$, Mann-Whitney U test, Fig. 3).

No fatal cases occurred. In children, parents reported of mild complaints after discharge like headache, backache and fatigue for 0 to 7 days (median 2 days; Düsseldorf cohort). After discharge, one of the parents had to

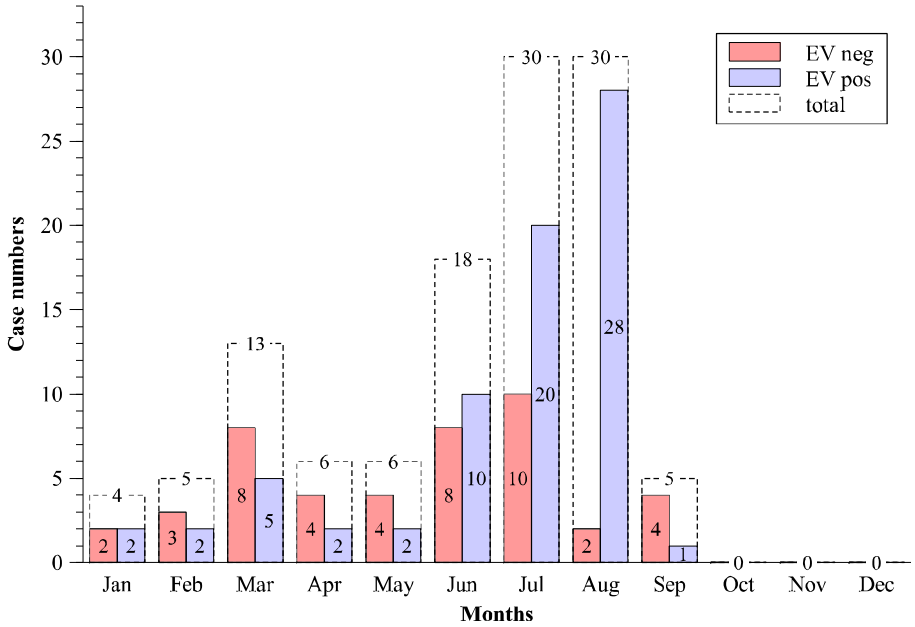

Fig. 1 Monthly distribution of meningitis cases in 2013 (Düsseldorf, Cologne, Berlin). These data were obtained from database query. Enterovirus (EV)-positive cases peaked from July to August in 2013

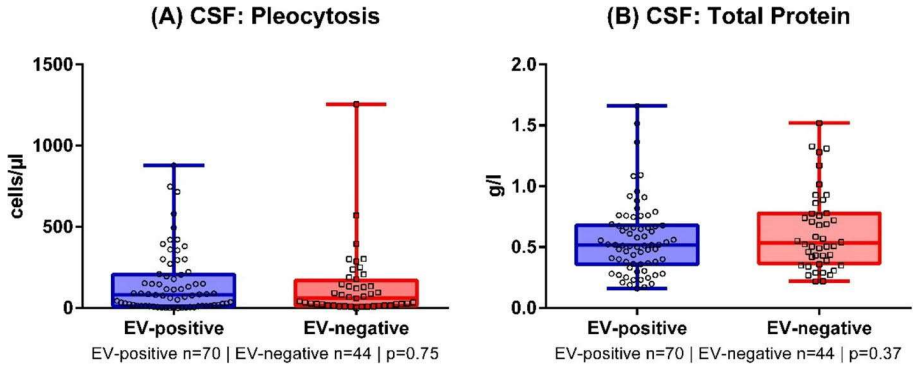

Fig. 2 Cerebrospinal fluid analysis of enterovirus (EV)-positive and EV-negative patients. No significant difference in cell count (**a**) and total protein (**b**). CSF = cerebrospinal fluid. Mann-Whitney *U* test

care for the children at home (0 to 5 days, median 3 days; Düsseldorf cohort).

Analysis of gender (Chi-Square-test of EV-positive vs. EV-negative patients, adults vs. children and hospitalization periods) did not reveal relevant differences.

Adults vs. children

A significantly higher ratio of children was found in the enterovirus-positive cohort, compared to the enterovirus negative group (38/72 vs. 4/45, Chi-Square-test, adj. $p < 0.001$). Children (both EV-positive and EV-negative) had a shorter period of hospitalization (adj. $p < 0.001$) and lower CSF protein levels than adults (adj. $p < 0.001$). There was no significant difference of CSF cell counts (Mann-Whitney *U* test, respectively).

An exclusive analysis of either adults or children did not reveal significant differences between EV-positive and EV-negative patients regarding age, duration of inpatient stay, CSF cell count and CSF total protein (Mann-Whitney *U* test, respectively). Numerical data of abovementioned comparisons are provided in Table 2.

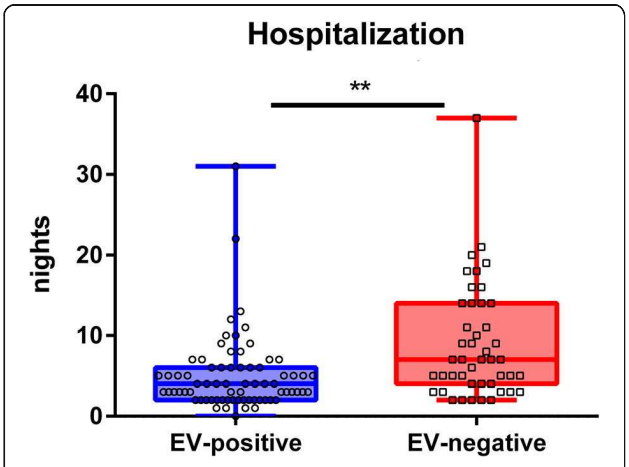

Fig. 3 Hospitalization analysis of enterovirus (EV)-positive ($n = 72$) and EV-negative patients ($n = 45$). Hospitalization of EV-negative patients is significantly longer ($p < 0.01$). Mann-Whitney *U* test

Predictors of hospitalization periods

In general, the duration of inpatient stay correlated with age (Spearman's Rho correlation coefficient 0.418, $p < 0.001$), CSF total protein (Spearman's Rho correlation coefficient 0.319, $p < 0.001$), and the delay from symptom onset to lumbar puncture (Spearman's Rho correlation coefficient 0.232, $p = 0.023$). For nominal variables, enterovirus status ($\eta = -0{,}32$) correlated with the duration of inpatient stay. In contrast, echovirus status, gender, and location (Neurological center the patient was treated) did not show a relevant correlation with the duration of the inpatient stay ($|\eta| < 0{,}3$).

Finally, a multivariate, stepwise linear regression was performed using the abovementioned variables (age, CSF cell count, CSF protein, delay between symptom onset and spinal tap enterovirus status, echovirus status, gender, treating center (Berlin, Cologne, Duesseldorf)). A total of three variables (age, CSF protein, and Echovirus status) were kept, which accounted for 30% of the variance of the hospitalization period (adjusted $R^2 = 0.302$, standardized Beta values: age = 0.354, CSF protein 0.247, and echovirus status − 0.169, respectively).

Therapy

The cases diagnosed with varicella zoster virus and herpes simplex virus 2 received specific therapy. No child received specific therapy in Düsseldorf.

RKI database query

An RKI database query (retrieved from https://evsurv.rki.de/) revealed a total of 3455 tested samples in 2013. 1242 of these cases were positive for EV, of which 672 cases were typed as echovirus 30. Therefore, our study includes 5.8% (72 of 1242 cases) of the reported EV-positive cases in Germany.

Table 2 Distribution of age, hospitalization, CSF cell count, and CSF protein for EV negative, EV positive, and all patients (Total). All groups are further subdivided by age into adults (ADU), children (PED), and all (Total) patients. *N* = number of patients, 75th perc. = 75th percentile, 25th perc = 25th percentile

	EV negative			EV positive			Total		
	ADU	PED	Total	ADU	PED	Total	ADU	PED	Total
Age (years)									
N	*41*	*4*	*45*	*34*	*38*	*72*	*75*	*42*	*117*
Range	64	10	77	56	17	74	66	17	84
75th perc.	50	14.75	48.5	40	9	32.75	44	9	38
median	36	8	36	33.5	5	15	36	6	26
25th perc.	30	7.25	28	24	0	3.25	27	0.75	8
Hospitalization (nights)									
N	*41*	*4*	*45*	*34*	*38*	*72*	*75*	*42*	*117*
Range	35.00	5	35	31.00	9.00	31	36.00	9.00	36
75th perc.	13	5	13	6	3.25	5	10	3.25	7
median	6	2	6	4	2.00	3	5	2	4
25th perc.	3.5	1.25	3	1.75	1	1	2	1	2
CSF cell count (cells/μl)									
N	*40*	*4*	*44*	*34*	*36*	*70*	*74*	*40*	*114*
Range	1255	100	1255	744	877	877	1255	877	1255
75th perc.	202.25	129.75	185.25	314.75	142	205	275.75	132.25	196.5
median	61.5	100	67	114.5	24.5	81	88	34.5	78
25th perc.	15.25	44.75	17.50	40.5	6.75	12	23.75	9.5	15
CSF protein (g/l)									
N	*40*	*4*	*44*	*34*	*36*	*70*	*74*	*40*	*114*
Range	1.30	0.64	1.30	1.29	0.73	1.51	1.66	0.73	1.65
75th perc.	0.78	0.79	0.78	0.80	0.57	0.68	0.78	0.58	0.74
median	0.53	0.42	0.53	0.65	0.34	0.52	0.56	0.36	0.52
25th perc.	0.39	0.23	0.36	0.48	0.25	0.35	0.43	0.250	0.36

Discussion

Enteroviruses are highly neurotropic and can manifest as meningitis, meningoencephalitis, poliomyelitis-like anterior myelitis, and Guillain-Barré syndrome [22, 23]. In our cohort, enteroviral infections were associated with meningitis. The prevalence of enteroviral meningitis is high worldwide (estimated 75,000 cases annually in the United States) [11], which makes this type of meningitis highly relevant to both caregivers and patients. We were able to show that the rate of infection peaks in the summer and early autumn months (June, July and August; Fig. 1). With age, the incidence of enteroviral meningitis decreases. Therefore, the incidence is highest in infants and toddlers [24], which was also the case in our cohort (Table 2).

The following findings and assumptions of our study are of significant interest, as they stress differences between EV-positive and EV-negative meningitis and may be of relevance for the treating physician: Overall, caregivers may expect shorter hospitalization times in EV-positive meningitis cases. Furthermore, routine CSF parameters that may already be determined in the emergency unit are not a sufficient tool to discriminate between EV-positive and EV-negative meningitis. When caregivers experience an unusual accumulation of aseptic meningitis cases in the summer and early autumn, patients should be tested for enterovirus infections and cases should be reported to the authorities. Contrary to previous studies regarding viral meningitis in general our data show that EV-positive meningitis is rather associated with a benign disease course.

In adult patients, the disease generally necessitates inpatient treatment for several days [25]. When children are affected, one parent may be incapacitated for a certain period of time to care for the child. In both cases, the disease may be associated with a temporary inability to work (either patient or parent). Because of the high number of cases per year, considerable costs arise for

society due to the loss of work and the necessary resources for medical treatment [26], although meningitis caused by enteroviruses usually has a relatively benign course.

To the best of our knowledge, the economic burden for society due to EV-positive meningitis has not been determined so far; and our data also provide just a limited insight, since we analyzed the duration of inpatient stay but did not assess any further inability to work.

Our data indicate that the course of EV-positive meningitis is predominantly benign, and that hospitalization time was significantly shorter in EV-positive, compared to EV-negative cases. This was also the case, when we did not consider the above-mentioned meningitis cases that received specific antiviral therapy (varicella zoster virus, herpes simplex virus 2). Moreover, a higher ratio of affected children and young adults were found in EV-positive cases. This could be explained by affected parents of young, diseased children. Hence, earlier convalescence in EV-positive groups may be explained by differences of age between both groups rather than different courses of the disease in general. In our cohort, routine CSF analysis (pleocytosis, protein level) is not a useful tool to discriminate between EV-positive and negative cases, but CSF protein level may correlate with length of stay in hospital.

Despite the generally excellent outcome of aseptic meningitis, there are rare instances of complicated courses that may lead to persistent neurological disability or even death [27–30]. Strategies for the systematic containment of endemic diseases are focused on ensuring hygienic measures to prevent the spread of viruses, as some weeks after illness, virulent pathogens can still be excreted via the feces.

In agreement with previous studies, enterovirus infections were detected as the most common cause for an aseptic meningitis in our cohort, driven by a high prevalence of echoviruses (52,8%). Indeed, our study demonstrates that voluntary reporting of diseases such as in this case can be an effective tool to better understand epidemiological details of certain diseases:

The mean age of EV-positive patients in our centers was 15 (3.25; 32.75) years, which accurately fits to previous data of Shandong [8] and Finland [9] (Finland 2009 15 years 8 months, Finland 2010 17 years 6 months, Shandong 2014 children within 15 years of age). The mean age of EV-negative pediatric patients (8 (7.25; 14.75) years) in our cohort was quite similar to that in a large South Korean pediatric cohort (8.4 ± 5 years) [31].

Conclusions

EV-positive epidemics are similar in terms of age and gender distribution and other factors worldwide. Overall, this entity remains a rather benign form of meningitis with a rather short length of stay in hospital, but may be associated with complicated courses that may lead to persistent neurological disability or even death. Routine CSF testing (pleocytosis, protein level) may not be suitable to distinguish EV-positive and EV-negative cases, but CSF protein level may correlate with hospitalization. Still, epidemics are a challenge for the health care system. Therefore, we recommend rigorous testing and reporting of aseptic meningitis cases. Within the National Enterovirussurveillance (EVSurv) all pediatric and neurological hospitals in Germany are offered free-of-charge enterovirus diagnostics in patients with suspected aseptic meningitis / encephalitis or acute flaccid paralysis. This health care concept is also well established in the US and led to a concise description of the disease burden [32].

Abbreviations

adj. p: Adjusted *p*-value; CDC: Centers for Disease Control and Prevention; CNS: Central nervous system; CSF: Cerebrospinal fluid; EV: Enterovirus; RKI: Robert Koch Institut; VZV: Varicella zoster virus

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Authors' contributions

JG* - study concept/design, acquisition/analysis/interpretation of data, drafting of the manuscript. CH* - study concept/design, acquisition/analysis/interpretation of data, drafting of the manuscript. HCL - acquisition/analysis/interpretation of data, revision of the manuscript. KR - acquisition/analysis/interpretation of data, revision of the manuscript. MK - acquisition/analysis/interpretation of data, revision of the manuscript. CS - acquisition/ analysis of data. OAdams - critical revision of the manuscript. CO - acquisition/analysis/interpretation of data, revision of the manuscript. HMB - acquisition/analysis/interpretation of data, revision of the manuscript. SD - acquisition/analysis/interpretation of data, revision of the manuscript. SB - acquisition/analysis/interpretation of data, revision of the manuscript. AS - critical revision of the manuscript. H-PH - critical revision of the manuscript. OAktas* - analysis/interpretation of data, and revision of the manuscript. PA* - Study concept/design, acquisition/analysis/interpretation of data, drafting and revision of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was approved by the ethics committee in Düsseldorf (registry number 4423). Due to the retrospective manner of this study, patient consent was waived by the ethics committee.

Consent for publication

Not applicable.

Competing interests

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HCL - declares no relevant competing interests.
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Publisher's Note

BRAIN COMMUNICATIONS

Relapse-independent multiple sclerosis progression under natalizumab

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The objective of this study was to investigate confirmed progression independent of relapse activity in relapsing-remitting multiple sclerosis patients under long-term natalizumab treatment. We performed a retrospective, cross-sectional study of clinical data captured between 1994 and 2019 at two German multiple sclerosis tertiary referral centres. Data files of all relapsing-remitting multiple sclerosis patients treated with natalizumab for ≥24 months were analysed. Confirmed progression independent of relapse activity was defined as ≥12 week confirmed disability progression on a roving Expanded Disability Status Scale reference score by 1 point in patients with an Expanded Disability Status Scale score ≤3 or 0.5 in patients with an Expanded Disability Status Scale score ≥3.5 in the absence of a relapse. Cox proportional hazard models were used to analyse the probability of developing confirmed progression independent of relapse activity depending on both disease and natalizumab treatment duration. Among the 184 patients identified, 44 (24%) developed confirmed progression independent of relapse activity under natalizumab irrespective of the Expanded Disability Status Scale score at natalizumab onset. Time to confirmed progression independent of relapse activity was not affected by Expanded Disability Status Scale at natalizumab onset (categorized by Expanded Disability Status Scale score ≤3.5 versus >3.5) nor by duration of disease nor by duration of therapy. Confirmed progression independent of relapse activity occurred earlier in the disease course in patients with an earlier natalizumab therapy onset with regard to disease duration. A stepwise forward regression analysis revealed disease duration as the main factor for confirmed progression independent of relapse activity development ($P = 0.005$). Taken together, confirmed progression independent of relapse activity occurs in a substantial proportion of patients on long-term natalizumab treatment and independent of Expanded Disability Status Scale score at natalizumab onset. Our findings suggest that patients who are initiated on natalizumab early during disease course, usually in order to treat an aggressive clinical phenotype, have a higher risk of early confirmed progression independent of relapse activity.

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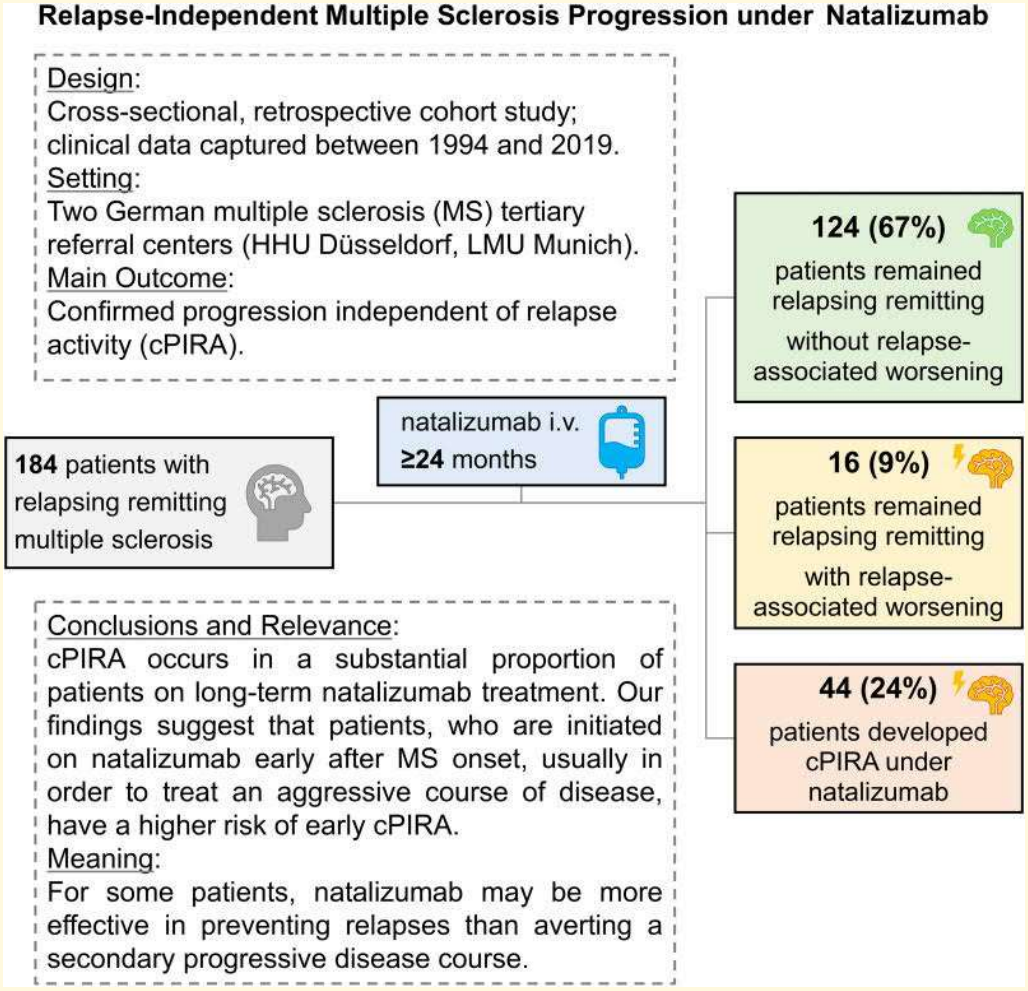
Keywords: multiple sclerosis; natalizumab; disease progression; cPIRA; long-term treatment

Abbreviations: ARR = annualized relapse rate; CDP = confirmed disability progression; cPIRA = confirmed progression independent of relapse activity; DMTs = disease modifying therapies; EDSS = Expanded Disability Status Scale; LMU = Ludwig-Maximilians University; MRZ = Measles Rubella and Varicella Zoster Reaction

Graphical Abstract



Introduction

Multiple sclerosis is an immune-mediated disease of the CNS with a complex, diverse disease course. Clinically, there are two different disease subtypes of multiple sclerosis: relapsing multiple sclerosis and progressive multiple sclerosis either manifesting itself as a primary progressive form with gradual worsening of neurologic disability from symptom onset or a secondary progressive disease course with or without (prior) relapse activity.[1] Pathologically, both inflammation and degeneration play an important role in both relapsing and progressive multiple sclerosis, and compartmentalized inflammation and degeneration in the CNS is considered to be of particular relevance in the progressive disease forms.[2] Natalizumab was early licensed as a disease modifying therapy (DMT) for the treatment of highly active relapsing remitting multiple sclerosis and its efficacy in reducing the relapse rate has been demonstrated in multiple studies.[3–8] However, natalizumab failed to meet the primary composite endpoint at 2 years in a phase 3 trial performed in secondary progressive multiple sclerosis.[9] A detailed analysis suggested a potential benefit in certain subtests, particularly for function of the upper extremities, and the open label extension demonstrated efficacy on the primary outcome at year three.[9] A possible explanation for the difference in efficacy of natalizumab in relapsing and progressive multiple sclerosis may be the inability to reach the compartmentalized pathology. To date, the effect of natalizumab on preventing conversion to secondary progressive

multiple sclerosis is still unclear. In a recently published prospective cohort, the number of natalizumab infusions was associated with a decrease of relapse rate, but no association was found with the progression of disability, the accumulation of lesion burden or the magnitude of brain volume loss, suggesting an uncertain benefit of prolonged natalizumab use on clinical and MRI outcomes of disease progression.[10] Another large real-world evidence study demonstrated that early natalizumab treatment during disease course reduced the risk of conversion to secondary progressive multiple sclerosis.[11]

We aimed to assess the relevance of relapse-independent disease progression as an indicator for secondary progressive multiple sclerosis conversion in two independent real-world cohorts of multiple sclerosis patients under long-term natalizumab treatment. It has to be kept in mind that there is still no consensus regarding the definition of secondary progressive multiple sclerosis. Among the most discussed guidelines are the Lublin criteria[1,12] and the secondary progressive multiple sclerosis definition developed by Lorscheider et al.,[13] but especially the time period of progression required for defining secondary progressive multiple sclerosis is heterogeneous in the literature.[14–17] In a large prospective study, long-term disability progression was associated with brain volume loss but not relapse rate.[18] The concept of progression independent of relapses (PIRA) has recently been introduced,[19] and that of confirmed progression independent of relapse activity (cPIRA) in combination with the use of a roving EDSS reference score may be an adequate approach for this unmet clinical need.

Materials and methods

Patients and recruitment

We conducted a retrospective chart review study at two centres: the Multiple Sclerosis Centers of the Heinrich-Heine-University Düsseldorf and of the Institute of Clinical Neuroimmunology, LMU Hospital, Ludwig-Maximilians University, Munich. We documented all relevant epidemiological, clinical and paraclinical information about the selected patients, such as age, sex, disease duration, relapses, Expanded Disability Status Scale (EDSS), MRI, previous and current therapies. The data were assessed during clinical routine visits and retrospectively collected from the hospital information system [MEDICO, Cerner/CGM (Düsseldorf)] and clinical charts (LMU Hospital). Inclusion criteria were diagnosis of relapsing remitting multiple sclerosis according to McDonald criteria 2010,[20] a continuous natalizumab therapy for $\geq$24 months, and availability of longitudinal EDSS and relapse data (at least three EDSS scores and information on relapse dates documented) for $\geq$24 months. The only exclusion criteria were cPIRA onset before natalizumab treatment and a disability change due to other causes than multiple sclerosis such as stroke, polyneuropathy or neurodegenerative disease leading to clinical impairment or deficit.

In this study, we used cPIRA as an indicator for secondary progressive multiple sclerosis conversion. It was defined as a $\geq$12 week confirmed disability progression (CDP) independent of relapse activity and evaluated in all patients including those who discontinued natalizumab therapy in the follow-up. Disability progression was defined as a worsening of 1 point on the EDSS in patients with a baseline EDSS $\leq$3 or 0.5 EDSS steps in patients with a baseline EDSS $\geq$3.5 in the absence of a relapse using a roving EDSS reference score.[21] We chose to define EDSS progression based on a cut-off value of 3.5 as EDSS steps up to 3.5 are mainly dominated by single functional system scores and rather sensitive to inter-rater variability, while from scores above 3.0 relevant disability in more than one system is required and above 4.0 the walking disability becomes increasingly relevant. The relapse-free interval relevant for cPIRA was defined as a time interval without relapses for a minimum of 12 consecutive months. All patients with an EDSS worsening according to the aforementioned definition of disease progression were included in the cPIRA group when the relapse unrelated EDSS worsening (PIRA) could be confirmed in the next clinical follow-up at least 12 weeks later (cPIRA). Relapses occurring after the development of cPIRA were classified as superimposed relapses (SIR).

To include a maximum of data and to analyse the relevance of events outside of the natalizumab treatment interval, we did not limit the follow-up length, but instead included all available EDSS and MRI data from the multiple sclerosis first diagnosis to the last documented visit. Therefore, cPIRA evaluation began with the first EDSS documented, e.g. at the time of multiple sclerosis diagnosis.

Relapse data were extracted from the clinical databases and by chart review. Relapses had been identified and classified during the clinical routine by experienced multiple sclerosis specialists at our tertiary referral centres based on patient interviews and clinical examination. Relapses were defined as a neurologic deficit compatible with an acute CNS inflammatory demyelinating event lasting at least 24 h in the absence of fever. Disability progression observed in visits with a relapse in between was considered as relapse-associated worsening (RAW) and not considered for analysis of cPIRA. Furthermore, in order to avoid the risk of carry over EDSS progression resulting from prior relapses, all follow-up intervals with relapse activity within one month prior to the baseline examination were excluded from the cPIRA analysis.

MRI activity was defined as presence of gadolinium enhancing lesions on T_1 imaging or the development of new or enlarging T_2 lesions in comparison to the previous MRI. MRI data and findings were collected retrospectively during the observational period. Owing to impaired comparability of different and non-standardized MRI protocols performed on different scanners in the clinical routine, we had to limit our analysis to the occurrence of inflammatory lesions and were not able to analyse brain volume and/or brain atrophy patterns.

Table 1 Demographic and clinical characteristics of the patients[a]

Baseline characteristics Medians (interquartile range)	Group 1: No-cPIRA[b] under natalizumab[c] ($n = 140$)	Group 2: cPIRA under natalizumab[c] ($n = 44$)	*P*-values[d] Group 1 vs Group 2
Age at natalizumab onset—year	33.5 (27; 42)	38.5 (29; 45)	n/s
Female sex—no (%)	92 (65.7)	26 (59.1)	n/s
Therapy duration natalizumab[e]—year	4.8 (3; 7.6)	5 (3; 9)	n/s
Disease duration since first manifestation—year	14 (10; 19)	18 (14; 25)	0.004 $r < 0.3$
Disease duration since first diagnosis—year	12 (9; 17)	15.5 (12; 19.8)	0.004 $r < 0.3$
Disease duration between first manifestation and natalizumab onset—year	6 (3; 11)	8 (3; 17)	n/s
Disease duration between first diagnosis and natalizumab onset—year	5 (2; 8)	4.5 (2; 12.5)	n/s
Number of other therapies[f]—no at study inclusion	3 (2; 4)	3 (2; 4)	n/s
Number of DMTs[g] prior to natalizumab—no	2 (1; 3)	2 (1; 3)	n/s
Annualized relapse rate under natalizumab[h]—no	0 (0; 0.3)	0 (0; 0.3)	n/s
Number of visits[i]—no	12 (8; 16)	16 (12; 22)	0.009 $r < 0.3$
EDSS[j]-change[k] in relapse free interval—no	0 (−0.5; 0)	1.5 (0.5; 2.5)	<0.001 $r > 0.5$

[a]Data include only patients who have been treated with natalizumab for a minimum of 2 consecutive years (main inclusion criterium) and whom EDSS values were available. All patient information is from the electronic database MEDICO (for the Düsseldorf Cohort) and from the patient files, which include clinical examinations and investigations results such as MRI findings, CSF and blood tests that have been collected before 01.01.2018 for the Düsseldorf cohort and before 07.08.2019 for the München cohort.
[b]Confirmed Disability Progression independent of Relapse Activity.
[c]The patient groups were defined as follows: patients who still experienced relapses during the observation time without EDSS worsening were included in the Group 1; Patients who developed a secondary progression under the natalizumab treatment were assigned to Group 2. The secondary progression was defined as an EDSS worsening of ≥1.0 point from the baseline EDSS score for patients with baseline score of 3.0 or less, or ≥0.5 for patients with baseline score of 3.5 or more that cannot be attributable to recent relapse activity. For each variable we provide the median of a given group with the corresponding interquartile range.
[d]*P*-values reflect Mann–Whitney U-test. A power analysis was conducted to obtain the correlation coefficient *r*. *P*-values for the comparison of Group 1 with Group 2 showed significant differences ($P < 0.05$) for the following variables: Disease duration since first manifestation, Disease duration since first diagnosis, Number of visits and EDSS-Change in relapse-free interval.
[e]The minimal natalizumab therapy duration is 2 years according to the inclusion criteria.
[f]This category includes all documented therapeutic measures from relapse-treatments to DMTs which have been taken since the first MS manifestation.
[g]Disease Modifying Therapies.
[h]Recorded between the first and the last recorded relapse in the period of time under natalizumab treatment.
[i]Meant is the number of visits which took place in the Universitätsklinikum Düsseldorf (UKD) or in the Universitätsklinikum München (LMU).
[j]Expanded Disability Status Scale.
[k]Recorded between the first and the last recorded EDSS value during the relapse-free period.

Statistical analysis

Statistical analyses were performed using SPSS 20 (IBM, Armonk, NY) and were run for all 184 patients included even if some of them stopped the natalizumab treatment and switched to another therapy during the follow-up. Table 1 summarizes the descriptive statistics listing the median and interquartile range for each variable of the different groups. A Mann–Whitney U-test was used to identify significant differences between the groups and a power analysis was conducted to define the correlation coefficient *r*. A Kruskal–Wallis test with Bonferroni *post hoc* test was used for to identify significant EDSS differences between groups. *P*-values below 0.05 were considered significant. A logistic regression analysis was performed to analyse which factors could have had an influence on cPIRA development in the overall cohort as well as in the single Munich and Düsseldorf cohorts separately. We opted for this regression model despite the risk of overfitting in order to decrease the chance of missing a signal from our defined variables. The following factors were included in the regression model: age and sex at natalizumab onset, the number and the class of DMTs prior to treatment with natalizumab as well as the duration of natalizumab therapy in years. DMTs were classified as first or second line as followed: as first line treatments we considered beta-interferon, glatiramer acetate, teriflunomide and dimethyl fumarate while second line treatments were mitoxantrone, alemtuzumab, fingolimod, natalizumab, rituximab, ocrelizumab and azathioprine. For the comparison of the demographic and clinical characteristics between the Düsseldorf and the Munich cohorts, we used the Mann–Whitney U two-sample rank-sum test. The probabilities of developing cPIRA were estimated using a Kaplan–Meier analysis. In order to facilitate interpretation and presentation of the results we divided the patients in equally sized subgroups based on the natalizumab treatment onset (≤8.6 years and >8.6 years), the EDSS score (≤3.5 and >3.5), the number of DMTs prior to natalizumab therapy onset (≤2 and >2) and the number of relapses that had occurred prior to the natalizumab treatment onset (<1, 1–2 and >2). Cox proportional hazard models correcting for age and sex reporting the hazard ratios [HR;

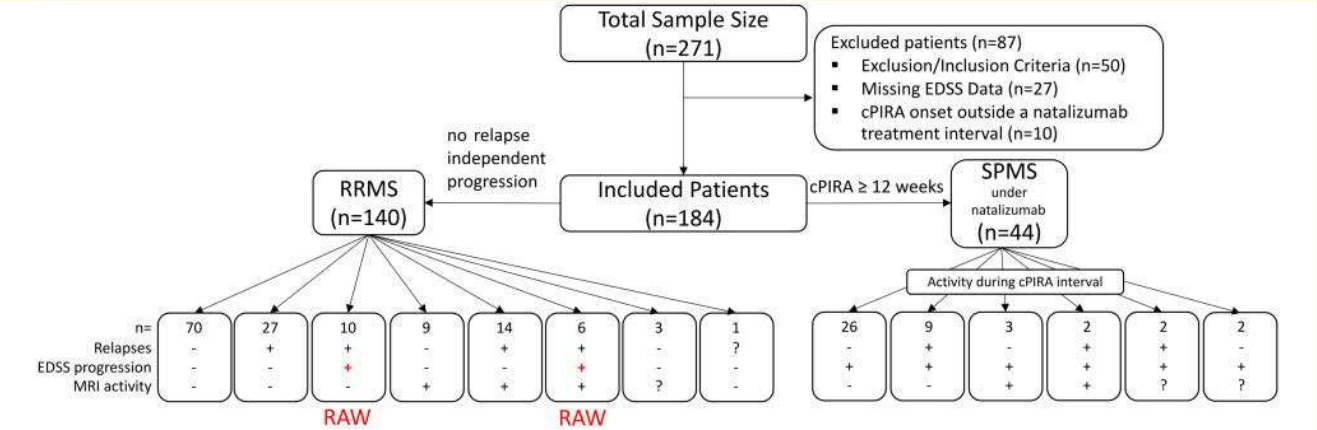


Figure 1 Overview of the total cohort. Flowchart of the total cohort. *In the confirmed progression independent of relapse activity (cPIRA) group, the '+' indicates the presence of relapse and MRI activity before or after the cPIRA defining interval.

Exp(B)] were used to compare the probability to develop cPIRA for these subgroups. Reporting followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline.

Ethics approval and consent to participate

The study was approved by the local ethics committee at the Heinrich Heine University of Düsseldorf (registry number 6083R) and at the Ludwig-Maximilians University Munich (Nr. 19116). Owing to the retrospective design of the study, informed consent was not necessary according to the local ethics committee.

Data availability statement, responsibility and analysis

Philipp Albrecht, the corresponding author, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The datasets supporting the conclusions of this article are included within the article and its additional files. Raw data generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Results

Comparison of the cPIRA rate depending on baseline parameters

Out of the 271 relapsing remitting multiple sclerosis patients identified with natalizumab therapy at the two investigating centres (Figs 1 and 2, Table 1 and Supplementary Table 1), 184 patients met the inclusion criteria, while 77 were excluded from the data analysis

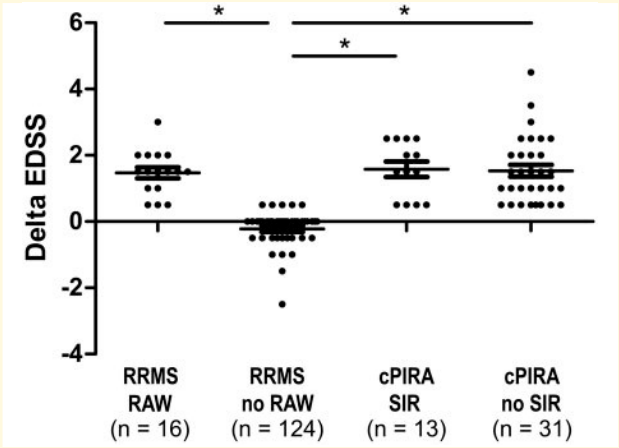


Figure 2 Disability change of the total cohort. EDSS change of confirmed progression independent of relapse activity (cPIRA) patients [with and without superimposed relapses (SIR)] and relapsing remitting multiple sclerosis patients [with and without relapse-associated worsening (RAW)], *$P < 0.05$, Kruskall–Wallis with Bonferroni post hoc test.

due to lack of EDSS and relapse data (27) or insufficient follow-up data (≤24 months of natalizumab therapy) (50). Furthermore, 10 patients were excluded due to cPIRA onset outside a natalizumab treatment interval, e.g. before initiation of natalizumab or development of cPIRA during a pause of natalizumab treatment. Of these 184 patients, 140 patients remained relapsing remitting (76%), while 44 developed cPIRA as an indicator for secondary progressive multiple sclerosis (24%). Under the 140 relapsing remitting patients, 16 patients (9%) presented a relapse-associated worsening (RAW) with relevant EDSS increase. The median time on natalizumab therapy until cPIRA occurred was 10 ± 1 years.

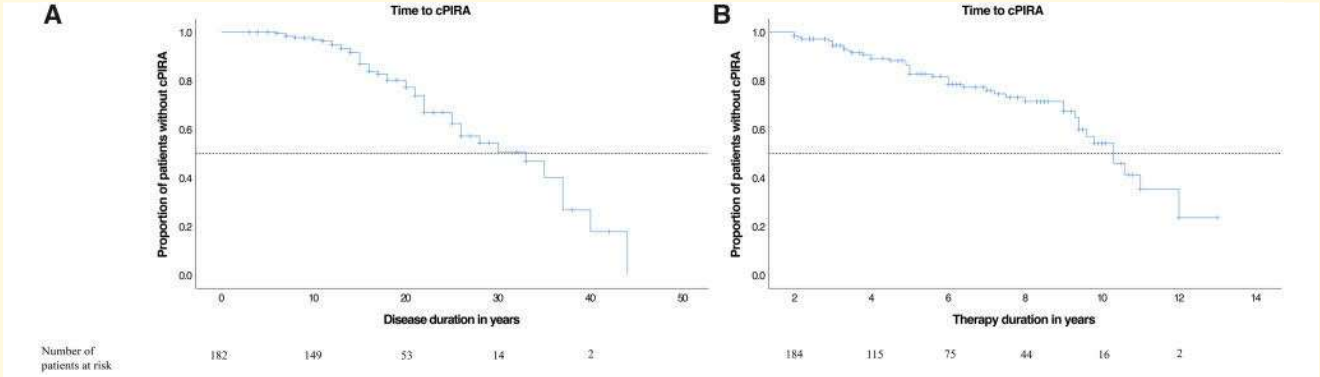


Figure 3 Kaplan–Meier curves of the total cohort. (**A**) Kaplan–Meier curves for the time (in years) of disease duration from the first multiple sclerosis manifestation and (**B**) natalizumab treatment duration until the outcome confirmed progression independent of relapse activity (cPIRA) occured. cPIRA was defined as an EDSS increase of $\geq$1.0 point from the baseline EDSS score for patients with baseline score of 3.0 or less, or $\geq$0.5 for patients with baseline score of 3.5 or more.

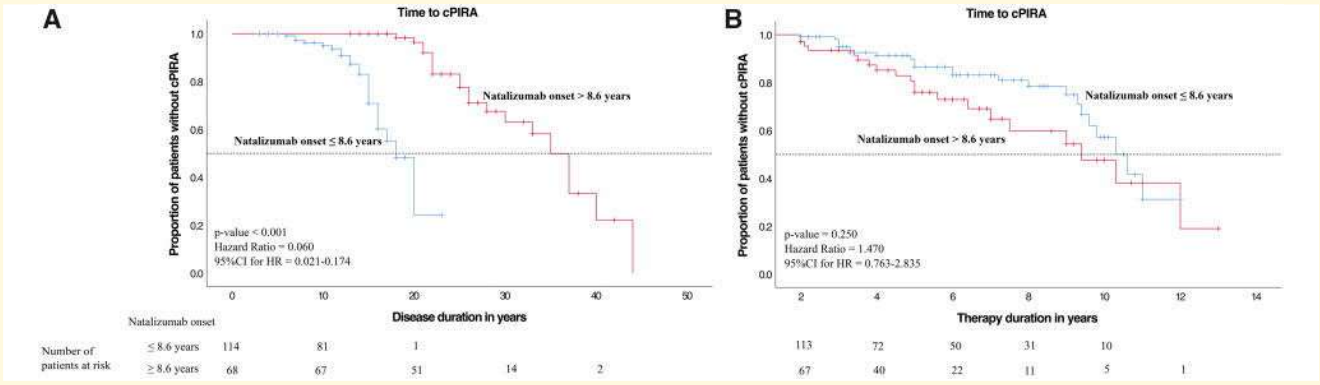


Figure 4 Kaplan–Meier curves of the total cohort, disease duration at natalizumab onset subanalysis. (**A**) Kaplan–Meier curve for the time of disease duration and (**B**) natalizumab therapy duration (in years) to onset of confirmed progression independent of relapse activity (cPIRA). Progression free survival in the patients with natalizumab therapy onset is compared within (blue curve) and after (red curve) 8.6 years from multiple sclerosis first manifestation to first natalizumab dose. The discriminatory value of 8.6 years corresponds to the mean duration between the first multiple sclerosis manifestation and the first received natalizumab dose of the total cohort. *P*-values for the comparison of the two groups were obtained with Cox proportional hazard models correcting for age and sex.

Investigation of factors responsible for time to cPIRA

Information on MRI activity was available for all patients but not for all follow-up intervals due to the heterogeneity of follow-up in the real-world setting. Approximately half of the 184 included patients had neither MRI nor relapse activity, and patients with relapses and MRI activity were less common (Fig. 1). In the No-cPIRA under natalizumab group, 70 of 140 patients (50%) had neither relapse nor MRI activity, as compared to 26 of 44 patients (59%) in the cPIRA under natalizumab group. On the other hand, 20 of 140 patients (14.3%) in the No-cPIRA under natalizumab and 2 of 44 patients (4.5%) in the cPIRA under natalizumab group had both MRI and relapse activity. Overall, disease duration was significantly longer, the number of hospital visits prior to natalizumab and the increase of EDSS in the relapse-free period were significantly higher in patients with cPIRA under natalizumab compared to No-cPIRA patients (Table 1). The EDSS remained stable and showed a tendency to improvement in No-cPIRA relapsing remitting multiple sclerosis patients without RAW (mean change of -0.2 ± 0.6 over a mean of 5.5 years) while patients who developed cPIRA with and without superimposed relapses (SIR) as well as relapsing remitting multiple sclerosis patients with RAW (Fig. 1) presented a significant deterioration of EDSS with a mean of 1.5 ± 0.9 over a mean of 5.8 years (Fig. 2). A significant difference with regards to MRI and CSF parameters was not detected (Supplementary Table 1). The regression analysis revealed disease duration as the main factor for cPIRA development ($P = 0.005$). Other factors (like sex, age, class of treatment and number of prior therapies as well as natalizumab therapy duration) had no additional influence on the development of cPIRA.

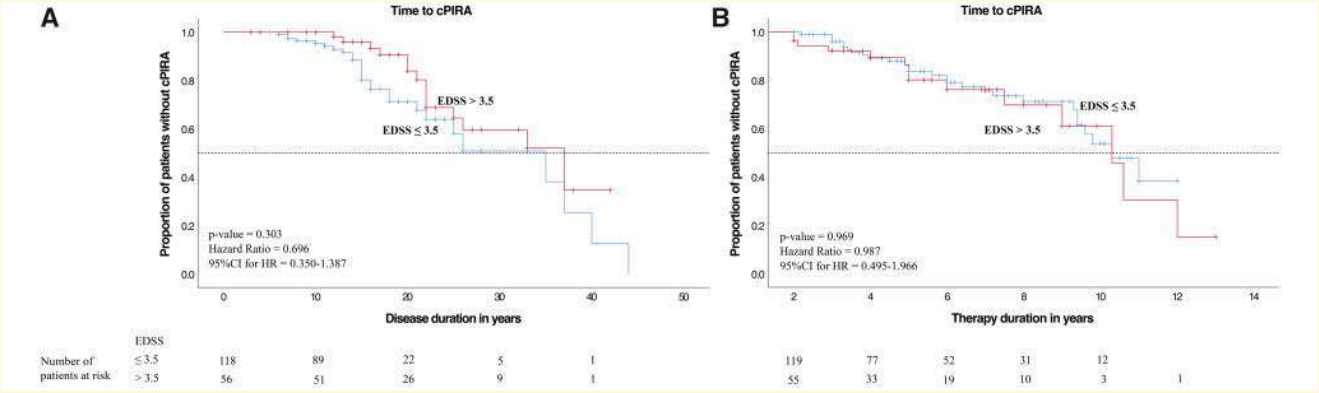


Figure 5 Kaplan–Meier curves of the total cohort, diseases severity subanalysis. (**A**) Kaplan–Meier curve for the time of disease duration and (**B**) natalizumab therapy duration (in years) to onset of confirmed progression independent of relapse activity (cPIRA). The analysis was performed after the patients have been divided into two groups according to the EDSS Score performed at the time of natalizumab therapy onset. The red curve represents the patients with an EDSS score greater than 3.5, while the blue curve the patients with an EDSS score of 3.5 or less. *P*-values for the comparison of the two groups were obtained with Cox proportional hazard model correcting for age and sex.

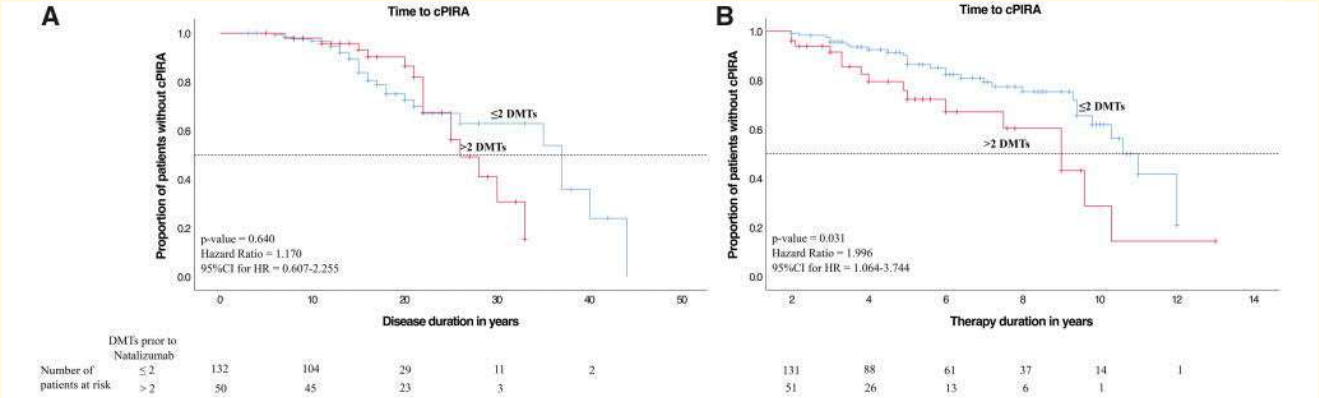


Figure 6 Kaplan–Meier curves of the total cohort, previous treatment subanalysis. (**A**) Kaplan–Meier curve for the time of disease duration and (**B**) natalizumab therapy duration (in years) to onset of confirmed progression independent of relapse activity (cPIRA). Compared is the progression free survival in the patients with less (blue curve) and more (red curve) than 2 DMTs prior to natalizumab therapy onset. *P*-values for the comparison of the two groups were obtained with Cox proportional hazard model correcting for age and sex.

Cox proportional hazard models were used to compare the cPIRA-free survival between subgroups over time (Figs 3–7), and the number of remaining patients under observation at a given timepoint are indicated as 'patients at risk' below the *x*-axes in Figs 3–7. cPIRA occurred earlier in the course of disease in patients with an earlier onset of natalizumab therapy [≤8.6 versus >8.6 years, $P < 0.001$, HR Exp(B) = 0.060, 95%CI = 0.021–0.174] but considering only the time on natalizumab the onset of cPIRA did not differ between both groups [$P = 0.250$, HR Exp(B) = 1.470, 95%CI = 0.763–2.835]. Time to cPIRA did not differ between patients with EDSS ≤3.5 and >3.5 neither considering the duration of disease [$P = 0.303$, HR Exp(B) = 0.696, 95%CI = 0.350–1.387] nor the duration of therapy [$P = 0.969$, HR Exp(B) = 0.987, 95%CI = 0.495–1.966]. Furthermore, patients with >2 DMTs before natalizumab show no difference in the development of cPIRA over the disease course with respect to patients with ≤2 DMTs [$P = 0.640$, HR Exp(B) = 1.170, 95%CI = 0.607–2.255]. However, considering only the period of natalizumab therapy, patients with >2 DMTs prior to natalizumab developed cPIRA significantly earlier than patients with ≤2 DMTs [$P = 0.031$, HR Exp(B) = 1.996, 95% CI = 1.064–3.744]. The annualized relapse rate (ARR) did not differ between patients who developed cPIRA and those who did not. However, the mean EDSS deterioration was significantly higher in natalizumab treated patients who developed cPIRA (Fig. 2).

An overview of the Düsseldorf and Munich cohorts including separate sub-analyses is provided in Supplementary Table 2 (for the subgroup of cPIRA patients under natalizumab) and Supplementary Fig. 1.

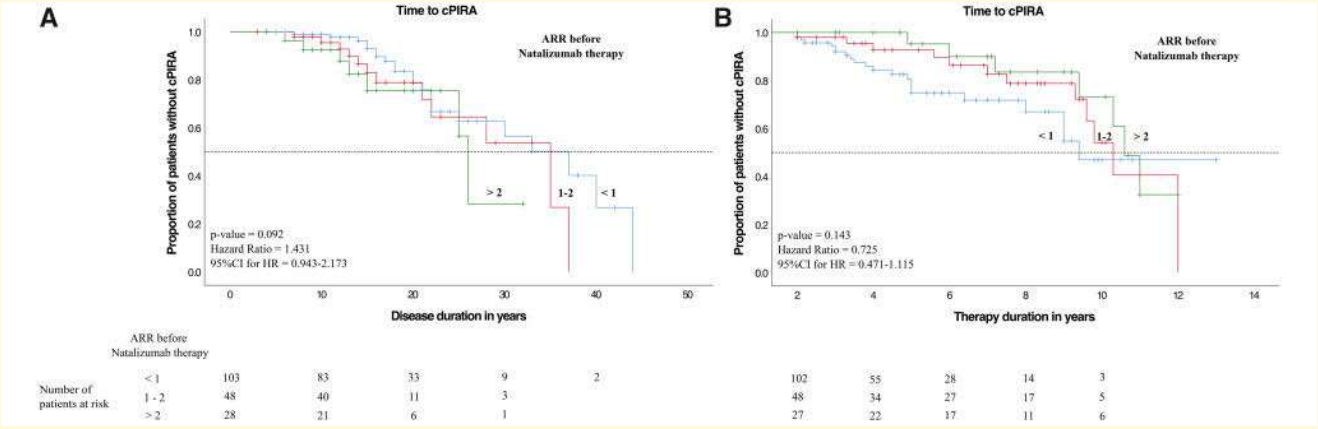


Figure 7 Kaplan–Meier curves of the total cohort, relapse rate subanalysis. (**A**) Kaplan–Meier curve for the time of disease duration and (**B**) natalizumab therapy duration (in years) to onset of confirmed progression independent of relapse activity (cPIRA). The survival analysis was performed for subgroups stratified based on the rate of annualized relapse rate (ARR) prior to natalizumab treatment onset. *P*-values for the comparison of the groups were calculated with Cox proportional hazard model correcting for age and sex.

Comparing the Düsseldorf and Munich cohorts revealed significant differences regarding the time between first manifestation and first diagnosis, current therapy, Measles Rubella and Varicella Zoster (MRZ)-reaction and natalizumab discontinuation, but no differences regarding age, sex, EDSS at first diagnosis and disease duration. A stepwise forward regression analysis revealed that no variable influenced the occurrence of cPIRA in the Munich cohort while for the Düsseldorf cohort age and prior therapies had a significant influence on secondary progressive multiple sclerosis development. In the Munich cohort, 14 of 70 included patients (20%) and in the Düsseldorf cohort, 30 out of 114 included patients (26.3%) developed secondary progressive multiple sclerosis according to our cPIRA definition (Supplementary Fig. 1). We observed no significant difference regarding the EDSS change between the Munich and Düsseldorf cohorts.

Discussion

With over a decade of experience treating multiple sclerosis patients with natalizumab, it is now possible to explore the long-term effects in a real-world setting. Our study indicates that natalizumab does not change disability progression in progressive MS, which is in line with the results from a randomized controlled phase 3 trial.[9]

Interestingly, a recent pooled analysis of phase 3 relapsing remitting multiple sclerosis trials revealed that most of the accumulated disease progression is not relapse-associated.[22] Furthermore, data from the Tysabri® Observational Program (TOP) suggest that the probability of disability worsening under natalizumab is 27.8%.[23] In our study, we applied a modified version of the PIRA concept[19,22] with confirmation of disability progression at a variable timepoint >12 weeks after the previous assessment. Furthermore, we defined progression as an EDSS increase of 0.5 points beyond 3.5 and not beyond 5.5 as used in previous studies.[19,22] This may be interpreted as a limitation for reason of comparability. However, we consider the phase of moderate disability with EDSS 3.5–5.5 to be particularly relevant for cPIRA development and therefore chose to increase the sensitivity for change in this range.

Overall, our findings are in line with previous studies.[22,23] Since these findings have not been directly correlated, caution is required to imply a cause-and-effect relationship.

Our data suggest that almost 80% of patients do not develop cPIRA and remain stable despite a mean disease duration of 15.6 ± 7.5 years. Of note, natalizumab was not completely ineffective in a phase 3 secondary progressive multiple sclerosis trial as it may positively influence upper limb function.[9] However, more than 20% of our patients did develop cPIRA and by definition, the EDSS of these patients increased under natalizumab with mean change of 1.4 ± 0.9 compared to baseline. When comparing our results with existing natural disease course data, the rate for conversion to a secondary progressive disease course may be reduced by 50% under natalizumab.[14,24,25] However, the secondary progressive multiple sclerosis conversion rate in our study was not inferior to the rates reported for other DMTs.[26–28] As natalizumab failed to reduce EDSS progression in a phase 3 secondary progressive multiple sclerosis trial,[9] its mechanism of preventing leukocyte trafficking may not be of sufficient relevance for halting progression. Moreover, the relevance of preventing relapses in order to prevent secondary progressive multiple sclerosis may not be as relevant as expected.[29]

In a recent real-world evidence study on the long-term effects of immunotherapies,[11] secondary progressive multiple sclerosis conversion was significantly lower in

natalizumab-treated patients, as compared to untreated patients. Considering our data, this effect may rather be associated with disease duration. The exact reasons for cPIRA under natalizumab despite good control of relapses remain open. The positive effect on progression reported for siponimod versus placebo[30] suggests that tissue penetrance may be of relevance, e.g. to target CNS resident cells such as microglia. More mechanistic studies comparing therapeutics and including advanced imaging and biomarkers are warranted. Basic MRI and CSF may not be suitable to determine patients' risk for developing cPIRA. Neuroimaging studies suggest that the estimated rate of lesion growth[31] and of atrophied brain T2 lesion volume[32,33] are associated with secondary progressive multiple sclerosis conversion risk. However, our study is limited by its retrospective design and by an indication bias favouring more active patients to receive natalizumab. Furthermore, 32% (87 of 271) patients were excluded due to inclusion/exclusion criteria and missing EDSS data, and our study design does not allow us to account for these patients. This dropout rate is due to the fact that patients often decide to receive natalizumab treatment in a private practice setting and sometimes do not return to the university centres. We do not expect these to have a different course and therefore do not anticipate a major source of bias.

The different patient cohorts described in studies mentioned above cannot be compared. As disease duration was the only factor influencing cPIRA in our cohort, we cannot postulate a clear treatment associated mechanism. The fact that we investigated cPIRA in data obtained in clinical routine without standardized follow-up intervals and heterogeneous treatment duration bares the risk of bias.

One may assume that patients with a severe disease course are more likely to visit the outpatient clinic more frequently compared to clinically stable patients, which may lead to cPIRA overestimation. However, for all patients presenting confirmed EDSS progression information on relapse activity was available and therefore cPIRA and RAW could be evaluated. On the one hand, both cPIRA patients with and without SIR showed a significant EDSS increase compared to relapsing remitting multiple sclerosis patients without RAW. On the other hand, we have to acknowledge that RAW may be underrepresented since 10 patients form our centres with relapse activity discontinued natalizumab before reaching 24 months of follow-up and therefore did not meet the inclusion criteria.

In our cohort, cPIRA risk was not different between the EDSS ≤ 3 and ≥ 3.5 group. Therefore, a bias resulting from differential sensitivity in high and low ranges of the EDSS scoring system seems rather unlikely as relapse independent disease progression was equally distributed in these groups. Furthermore, using CDP at week 24 did not change the main result.

A strength of our study is the real-world setting with long follow-up times in two independent cohorts. We acknowledge that a comparison to patients on other long-term treatment would be of highest interest. In context with previous studies,[21,22] we cannot exclude that mild exacerbations which do not fulfil the relapse definition may be a cause of cPIRA.

Our data suggest that patients with early natalizumab initiation (≤ 8.6 years after diagnosis) seem to be more likely to develop cPIRA than those with late initiation (Fig. 4A). However, since natalizumab therapy duration had no influence on progression regardless of the timing of initiation (Fig. 4B), we interpret this finding to be driven by disease severity: Patients with a severer disease course may receive natalizumab earlier.

The fact that 20% of our patients developed cPIRA highlights the need for close monitoring of clinical disability in patients under long-term natalizumab treatment as therapeutic consequences may be considered.

Supplementary material

Supplementary material is available at *Brain Communications* online.

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Competing interests and conflict of interest

J.G. received travel/meeting/accommodation reimbursements from Biogen, Merck Serono, Sanofi-Genzyme, Grifols, and a Research Fellowship from the Deutsche Forschungsgemeinschaft (project number 438899010, GZ: GR 5665/1-1). V.I.L. received fees for speaking from Biogen, Genzyme, and Novartis and research support from Novartis. G.S. declares no relevant competing interests. K.L. declares no relevant competing interests. I.M. received travel expenses from MedDay and Roche Pharma, and compensation from Serono for participation in an advisory board. T.K. received travel expenses and speaker honoraria from Bayer Healthcare, Teva Pharma, Merck, Novartis Pharma, Sanofi-Aventis/Genzyme, CLB Behring, Roche Pharma and Biogen as well as grant support from Bayer-Schering AG, Novartis and Chugai Pharma. S.G.M. received honoraria for lecturing and travel expenses for attending meetings from Almirall, Amicus Therapeutics Germany, Bayer Health Care, Biogen, Celgene, Diamed, Genzyme, MedDay Pharmaceuticals, Merck Serono,

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Disease-Modifying Drug Uptake and Health Service Use in the Ageing MS Population

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Background: Evidence regarding the efficacy or effectiveness of the disease-modifying drugs (DMDs) in the older multiple sclerosis (MS) population is scarce. This has contributed to a lack of evidence-based treatment recommendations for the ageing MS population in practice guidelines. We examined the relationship between age (<55 and ≥55 years), DMD exposure and health service use in the MS population.

Methods: We conducted a population-based observational study using linked administrative health data from British Columbia, Canada. We selected all persons with MS and followed from the most recent of their first MS or demyelinating event, 18th birthday or 01-January-1996 (index date) until the earliest of emigration, death or 31-December-2017 (study end). We assessed DMD exposure status over time, initially as any versus no DMD, then by generation (first or second) and finally by each individual DMD. Age-specific analyses were conducted with all-cause hospitalizations and number of physician visits assessed using proportional means model and negative binomial regression with generalized estimating equations.

Results: We included 19,360 persons with MS (72% were women); 10,741/19,360 (56%) had ever reached their 55th birthday. Person-years of follow-up whilst aged <55 was 132,283, and 93,594 whilst aged ≥55. Any DMD, versus no DMD in the <55-year-olds was associated with a 23% lower hazard of hospitalization (adjusted hazard ratio, aHR0.77; 95%CI 0.72-0.82), but not in the ≥55-year-olds (aHR0.95; 95%CI 0.87-1.04). Similar patterns were observed for the first and second generation DMDs. Exposure to any (versus no) DMD was not associated with rates of physician visits in either age group (<55 years: adjusted rate ratio, aRR1.02; 95%CI 1.00-1.04 and ≥55 years: aRR1.00; 95% CI 0.96-1.03), but variation in aRR was observed across the individual DMDs.

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Conclusion: Our study showed beneficial effects of the DMDs used to treat MS on hospitalizations for those aged <55 at the time of exposure. In contrast, for individuals ≥55 years of age exposed to a DMD, the hazard of hospitalization was not significantly lowered. Our study contributes to the broader understanding of the potential benefits and risks of DMD use in the ageing MS population.

Keywords: ageing, cohort studies, disease-modifying drugs, health services, hospitalization, multiple sclerosis, physician services

INTRODUCTION

Multiple sclerosis (MS) is a chronic, immune-mediated disease characterized by demyelination and neurodegeneration affecting both brain and spinal cord. While most people will be diagnosed with MS between the ages of 20-50 years, the average age range of people living with MS in North America is between 55 and 65 years (1, 2). Despite this, people with MS aged 55 years or older have often been excluded from clinical trials testing the efficacy of disease-modifying drugs (DMDs) (1–4). While short-term MS clinical trials showed limited benefits of taking DMD after age 53 years (5), and the potential for harm (e.g., higher neoplasm risk, especially after age 45 years) (6), all based on meta-analyses, the evidence regarding the long-term efficacy or effectiveness and safety profile of DMDs in the older MS population is scarce (7, 8). This has contributed to a lack of treatment recommendations for the ageing MS population in practice guidelines (3, 4).

Health administrative data which captures health care use information offers opportunity to assess the real-world effectiveness of the DMDs used to treat MS. This approach has been successfully applied to examine the safety and effectiveness of the DMDs in the general, or healthcare insured, MS population (9–13).

In this study, we accessed population-based health administrative data captured over a 22-year period in the province of British Columbia, Canada, to examine the relationship between age (<55 and ≥55 years), DMD exposure and health service use in the MS population. We examined age as a dynamic process for each person, by dividing the individual's time spent before and after reaching age 55 years.

MATERIALS AND METHODS

Data Sources

We conducted a population-based observational study using linked administrative health data. These prospectively collected data covered the population of British Columbia, comprising 4.64 million residents, and representing around 13% of the Canadian population (14). The linked data comprised five datasets: (i) the provincial health insurance registry (15) providing demographic information for each individual, including sex, date of birth, residency status and location (three digit postal codes); (ii) vital statistics data (16) providing the date of death; (iii and iv) physician billing (17) and discharge abstract databases (18) capturing all physician visits and hospitalizations, with reasons for the visit or admission coded using the International Classification of Diseases (ICD)-9/10 system; and (v) the provincial prescription database (PharmaNet) (19) capturing all prescription drugs dispensed at outpatient and community pharmacies.

Study Population

We selected all persons with MS by using a validated algorithm with the cases defined as having at least 3 MS diagnostic codes (ICD-9/10 340/G35) in the hospital and/or physician data or an MS DMD record in the prescription data, as outlined previously (20–22). We assigned an index date to each person based on the most recent date of: the first MS or demyelinating event recorded in the hospital, physician or prescription data (**Supplementary Tables 1**, **2**), or 01-January-1996 (the date when the provincial prescription data first became available), or the person's 18th birthday. All persons required at least one year of residency in British Columbia before the index date, and were followed from the index date until the study end date defined as the earliest of emigration from the province, death or 31-December-2017.

We determined the cohort characteristics at the index date, including age, calendar year, sex, and socioeconomic status (reported as neighborhood-level income quintiles according to a person's three-digit postal codes by linkage to census data) (23). The burden of comorbidity was measured using a modified Charlson Comorbidity Index based on the diagnoses captured in the hospital and physician data during the one-year before the index date, with hemiplegia and paraplegia excluded to avoid misclassifying symptoms related to MS as comorbidity (24, 25).

DMD Exposure

The DMDs available during our study period (**Supplementary Table 2**) included the first generation DMDs – beta-interferon and glatiramer acetate, and the second generation DMDs – natalizumab, fingolimod, dimethyl fumarate, teriflunomide, alemtuzumab, daclizumab, and ocrelizumab. We grouped all beta-interferon products together as one class. We assessed DMD exposure status as a time-varying variable, initially as any versus no DMD, then by generation (first or second), and finally by individual DMDs. Neither daclizumab nor ocrelizumab were included in the assessment of individual DMDs due to the small number of individuals (<6) exposed over the study period, preventing the derivation of reliable estimates.

We determined the DMD exposure periods according to the number of days supplied for each individual DMD. A DMD was considered as being discontinued when there were no further

dispensations for the DMD for greater than 90 days. The discontinuation date was defined as the last DMD prescription fill date plus the number of days supplied, with a 30-day grace period applied (26). The exception was for alemtuzumab and ocrelizumab, whereby periods of exposure were defined as one year (for alemtuzumab) and six months (for ocrelizumab), from the date of first supply, plus a 30-day grace period if no further DMD fills occurred. Finally, as persons could not be on more than one DMD at the same time, once a person filled a new DMD prescription, then the previous DMD was considered discontinued. DMD exposure was assessed as a time-varying variable (i.e. a person's DMD exposure status was allowed to change over time).

Age Grouping

We assessed each person's current age as a time-varying variable, grouped as <55 or ≥55 years old. This age grouping was selected partly because older individuals (≥55 years) have often been excluded from enrolling in MS clinical trials (1–4), and partly because the prevalence of persons with MS aged 55 and above has risen in recent years (20, 27), such that these individuals represent a growing yet understudied group.

Outcomes

The outcome measures were all-cause hospitalizations and number of physician visits.

Hospitalization data included day surgery/minor procedures (but not drug infusions e.g., for natalizumab or alemtuzumab) (28). For the hospitalizations, any overlapping admissions or any new admission that occurred within one day of the previous hospitalization were counted as a single event (10, 29). For the physician visits, multiple claims with the same primary ICD code captured on the same day were counted as a single visit (10, 29). Neurologist visits were also excluded from the count as the number of these visits was anticipated to be higher in persons exposed to a DMD (versus no DMD) as part of routine care (4) (other physician specialties cannot prescribe an MS DMD in British Columbia). In addition, any pregnancy-related encounters (hospitalizations or physician visits based on the primary ICD code) were not included as an outcome as DMD cessation was expected to be common during pregnancy (4).

Statistical Analyses

We described the cohort characteristics at the index date by age group (<55 versus ≥55 years old at the index date) and DMD exposure (at any time during follow-up), using counts and percentages for the categorical variables, and means and standard deviations for the continuous variables. Person-years of follow-up by current age group at the time of exposure for each individual DMD was also reported.

We included an interaction term between DMD exposure and current age group (<55 or ≥55 years) at the time of follow-up to estimate the age-specific associations between DMD exposure and outcomes (all-cause hospitalizations and the number of physician visits). For each analysis, the period of 'no DMD exposure' was used as the reference category.

All-cause hospitalizations were assessed using proportional means models with robust sandwich variance estimates (30). Models were adjusted for sex, socioeconomic status (quintiles), age (continuous) and calendar year (continuous) at the index date, and for the Charlson comorbidity score, categorized as: 0, 1, 2, ≥3, and updated annually over time. The period of hospitalization was discounted from the follow-up time as a person could not be at risk of another hospitalization during the existing hospital stay. Findings were expressed as adjusted hazard ratios (aHRs) with the corresponding 95% confidence intervals (CIs).

The number of physician visits were examined using negative binomial regression models fitted by generalized estimating equations with an exchangeable working correlation matrix (31). The number of physician visits were calculated annually, or by DMD exposure periods when there were changes in DMD status within a year. An offset was included in the model to account for the variable length of time periods (log of person-time). Models were adjusted for sex and socioeconomic status (quintiles) at the index date, and the following covariates over time (updated on an annual basis) including age (continuous), Charlson comorbidity score (categorized as: 0, 1, 2, ≥3) and calendar year (continuous; to account for any secular changes in healthcare use). Findings were expressed as adjusted rate ratios (aRRs) with the corresponding 95% CIs.

A complementary analysis was also performed to describe the DMD exposure status for any person who had reached age 55 years at any time before the study end date.

We conducted the statistical analyses using SAS software version 9.4 (SAS Institute, Cary, NC, USA).

Study Registration and Ethical Approval

This study was registered with ClinicalTrials.gov (NCT04472975). We obtained ethics approval from the University of British Columbia's Clinical Research Ethics Board (H18-00407).

RESULTS

Cohort Characteristics

We identified a total of 19,360 persons with MS (72.0% were women). Almost half (44.1%, 8,533/19,360) of the cohort entered the study between 1996-1999, with the remainder entering between 2000-2017. The mean follow-up time was 11.7 years (SD 7.3). At the index date, 78.7% (15,235/19,360) were aged <55 years and 21.3% (4,125/19,360) were ≥55 years (**Table 1**). Of those aged <55 years at the index date, 29.7% (4,526/15,235) filled a DMD prescription during follow-up, whereas 5.0% (206/4,125) of persons aged ≥55 years at the index date did so. Within both age groups, those treated with an MS DMD were approximately 4-5 years younger relative to those who were untreated. For example, for those under age 55 years at the index date, the mean age was 36.1 years [SD 8.7] for those ever DMD exposed during follow-up, versus 40.5 years [SD 8.9] for those unexposed.

TABLE 1 | Characteristics of the multiple sclerosis study population by age group at the index date (<55 versus ≥55 years old) and by exposure to a disease-modifying drug at any time during follow-up, n=19,360.

Characteristics	Age at Index Date <55 Years, n=15,235		Age at Index Date ≥ 55 Years, n=4,125	
	DMD-Treated[a] n=4,526	Not Treated[a] n=10,709	DMD-Treated[a] n=206	Not Treated[a] n=3,919
Sex, n (%)				
Women	3,324 (73.4)	7,868 (73.5)	145 (70.4)	2,603 (66.4)
Men	1,202 (26.6)	2,841 (26.5)	61 (29.6)	1,316 (33.6)
Age at index date in years, mean (SD)	36.1 (8.7)	40.5 (8.9)	58.9 (4.6)	64.5 (8.0)
Socioeconomic status[b], n (%)				
1 (lowest income quintile)	876 (19.4)	2,037 (19.0)	38 (18.4)	812 (20.7)
2	839 (18.5)	2,075 (19.4)	31 (15.0)	750 (19.1)
3	953 (21.1)	2,149 (20.1)	39 (18.9)	790 (20.2)
4	958 (21.2)	2,311 (21.6)	48 (23.3)	777 (19.8)
5 (highest income quintile)	888 (19.6)	2,083 (19.5)	50 (24.3)	758 (19.3)
Unavailable	12 (0.3)	54 (0.5)	<6	32 (0.8)
Comorbidity score[c], n (%)				
0	3,820 (84.4)	8,552 (79.9)	154 (74.8)	2,525 (64.4)
1	553 (12.2)	1,585 (14.8)	35 (17.0)	806 (20.6)
2	121 (2.7)	388 (3.6)	11 (5.3)	335 (8.5)
≥ 3	32 (0.7)	184 (1.7)	6 (2.9)	253 (6.5)
Calendar year at index date, n (%)				
1996-1999	1,479 (32.7)	5,132 (47.9)	50 (24.3)	1,872 (47.8)
2000-2009	1,818 (40.2)	3,374 (31.5)	73 (35.4)	1,152 (29.4)
2010-2017	1,229 (27.2)	2,203 (20.6)	83 (40.3)	895 (22.8)
Follow-up[a] time in years,				
median (Q1, Q3)	12.2 (5.9, 18.6)	12.0 (5.4, 20.0)	8.2 (3.9, 13.3)	8.6 (4.0, 14.7)
mean (SD)	12.2 (7.0)	12.2 (7.5)	9.3 (6.5)	9.7 (6.6)
Number of different DMD prescriptions filled during the follow-up[a]				
1	2,865 (63.3)	N/A	171 (83.0)	N/A
2	1,194 (26.4)		30 (14.6)	
≥ 3	467 (10.3)		<6	
First DMD prescription, n (%)				
Beta-interferon[d]	2,833 (62.6)	N/A	122 (59.2)	N/A
Glatiramer acetate	1,080 (23.9)		48 (23.3)	
Natalizumab	63 (1.4)		<6	
Fingolimod	31 (0.7)		<6	
Dimethyl fumarate	300 (6.6)		13 (6.3)	
Teriflunomide	181 (4.0)		15 (7.3)	
Alemtuzumab	36 (0.8)		<6	
Daclizumab	<6		<6	
Ocrelizumab	<6		<6	
Number of individuals ever exposed, by type of DMD, during follow-up[a], n (%)				
First generation DMDs –any[e]	3,953 (87.3)	N/A	171 (83.0)	N/A
Beta-interferon[d]	3,016 (66.6)		124 (60.2)	
Glatiramer acetate	1,655 (36.6)		64 (31.1)	
Second generation DMDs – any[e]	1,703 (37.6)		53 (25.7)	
Natalizumab	277 (6.1)		9 (4.4)	
Fingolimod	416 (9.2)		<6	
Dimethyl fumarate	736 (16.3)		22 (10.7)	
Teriflunomide	497 (11.0)		23 (11.2)	
Alemtuzumab	178 (3.9)		<6	
Daclizumab	6 (0.1)		<6	
Ocrelizumab	<6		<6	

Key: SD, standard deviation; DMD, disease-modifying drug, N/A, not applicable.

As per data privacy and access agreements, small cell size (<6 individuals within any group) are suppressed.

[a]*Follow-up was from index date until the study end date (up to December 31st 2017).*

[b]*Socioeconomic status is reported by neighborhood income quintiles according to a person's three-digit postal codes (closest available to the index date).*

[c]*Comorbidity was measured using the modified Charlson Comorbidity Index (exclude hemiplegia/paraplegia to avoid misclassifying MS complications as comorbidity) based on the diagnoses captured in the hospital and physician data during the one-year before the index date.*

[d]*All beta-interferon products were grouped together as one class.*

[e]*Some people were exposed to >1 DMD; hence the sum of the individual first or second generation DMDs exceeds the sum of any first or second generation DMD.*

TABLE 2 | Person-years of follow-up in the multiple sclerosis cohort by each person's current age, grouped as <55 or ≥55 years old, and by disease-modifying drug exposure status.

Person-Years of Follow-Up	Person's Current Age	
	<55 Years [1]	**≥55 Years [2]**
During periods of exposure to:		
Any DMDs	20,555.5	4,414.8
Any first generation DMDs	17,180.4	3,842.8
Beta-interferon[a]	12,413.7	2,911.9
Glatiramer acetate	4,766.6	930.8
Any second generation DMDs	3,375.2	572.0
Natalizumab	745.6	85.5
Fingolimod	871.4	115.6
Dimethyl fumarate	1,051.0	195.4
Teriflunomide	489.0	168.5
Alemtuzumab	216.2	6.4
Daclizumab	<6	<6
Ocrelizumab	<6	<6
No DMD	111,727.6	89,179.3
Total person-years of follow-up	132,283.1	93,594.1

Key: DMD, disease-modifying drug.

[a]*All beta-interferon products were grouped together as one class.*

Total cohort size=19,360. Of these, by the study end n=10,741/19,360 (55.5%) had ever reached their 55th birthday, with n=4,125/10,741 (38.4%) doing so by the index date and n=6,616/10,741 (61.6%) during follow-up. The remainder, n=8,619/19,360 (44.5%) never reached their 55th birthday by the study end. Thus, n=6,616 individuals contributed follow-up time to both columns [1] and [2], n=8,619 only to column [1] and n=4,125 only to column [2].

Irrespective of DMD exposure status during follow-up, the comorbidity burden (measured using the modified Charlson Comorbidity Index) was lower for persons <55 years at the index date, relative to those ≥55 years old. With respect to DMD exposure status, the comorbidity burden at the index date was lower in the DMD-treated group compared to the non-treated group. For example, for those age ≥55 years at the index date, 52/206 (25.2%) had a comorbidity in the DMD-treated group, versus 1,394/3,919 (35.6%) in the non-treated group. The socio-economic quintiles were generally evenly distributed across all four groups (**Table 1**).

Of those ever filling a DMD prescription during follow-up, the proportion exposed to a first generation DMD was similar regardless of age at the index date. Whereas, a higher proportion of the younger (<55 years) MS cases were exposed to a second generation DMD (37.6%, 1,703/4,526), compared to older individuals (≥55 years; 25.7%, 53/206). A higher proportion of younger persons with MS (<55 years at the index date) also switched between DMDs at least once during follow-up (36.7%; 1,661/4,526), compared to older individuals (≥55 years; 17.0%, 35/206).

As younger persons (<55 years) could transition to the older age group (≥55 years) throughout our >20-year study period, an overview of the person-years of follow-up by each person's current age group and DMD exposure status is shown in **Table 2**. Not unexpectedly, the number of person-years of follow-up was higher in persons with a current age of <55 (versus ≥55 years), irrespective of DMD exposure status. Of note the person-years of follow-up for certain DMDs were modest particularly in the older (≥55 years) age group.

Hospitalizations

Any DMD, relative to no DMD, was associated with a 23% lower hazard of hospitalization for those aged <55 years at the time of DMD exposure (aHR 0.77; 95%CI 0.72-0.82), but was not for those aged ≥55 years (aHR 0.95; 95%CI 0.87-1.04), **Figure 1**. Similar trends were observed for the first generation DMDs, where a 22% significantly lower hazard was observed for those aged <55 years, and, for the second generation DMDs, a 27% significantly lower hazard. Neither of these findings reached significance for those aged ≥55 years at the time of DMD exposure, where the lower hazard ranged from 3% to 20%. When the DMDs were assessed individually, the hazard of hospitalization for those aged <55 years at the time of exposure ranged from a 9% lower hazard for natalizumab, to 10% for alemtuzumab, 18% for glatiramer acetate, 24% for beta-interferon, 30% for dimethyl fumarate, 34% for teriflunomide, and 37% for fingolimod. All reached statistical significance, except for natalizumab and alemtuzumab, although the 95% confidence intervals were also very wide for these two DMDs. For person's aged ≥55 years at the time of DMD exposure, the corresponding HRs did not reach significance, except for fingolimod, which was associated with a 37% lower hazard of hospitalization. All results for the DMD exposure and hospitalizations analyses by age group are shown in **Figure 1**.

Physician Visits

While exposure to any DMD (versus no DMD) was not associated with altered rates of physician visits in either age group (<55 years: aRR 1.02; 95%CI 1.00-1.04 and ≥55 years: aRR 1.00; 95%CI 0.96-1.03), variation was observed across the individual DMDs (**Figure 2**). A 27-33% higher rate of physician visits was observed during exposure to a second generation DMD, alemtuzumab, reaching significance in the younger, but not older population. In contrast, exposure to another second generation DMD, fingolimod was associated with a significantly lower rate of physician visits, by 12%, for those <55 years. More modest differences were seen for the first

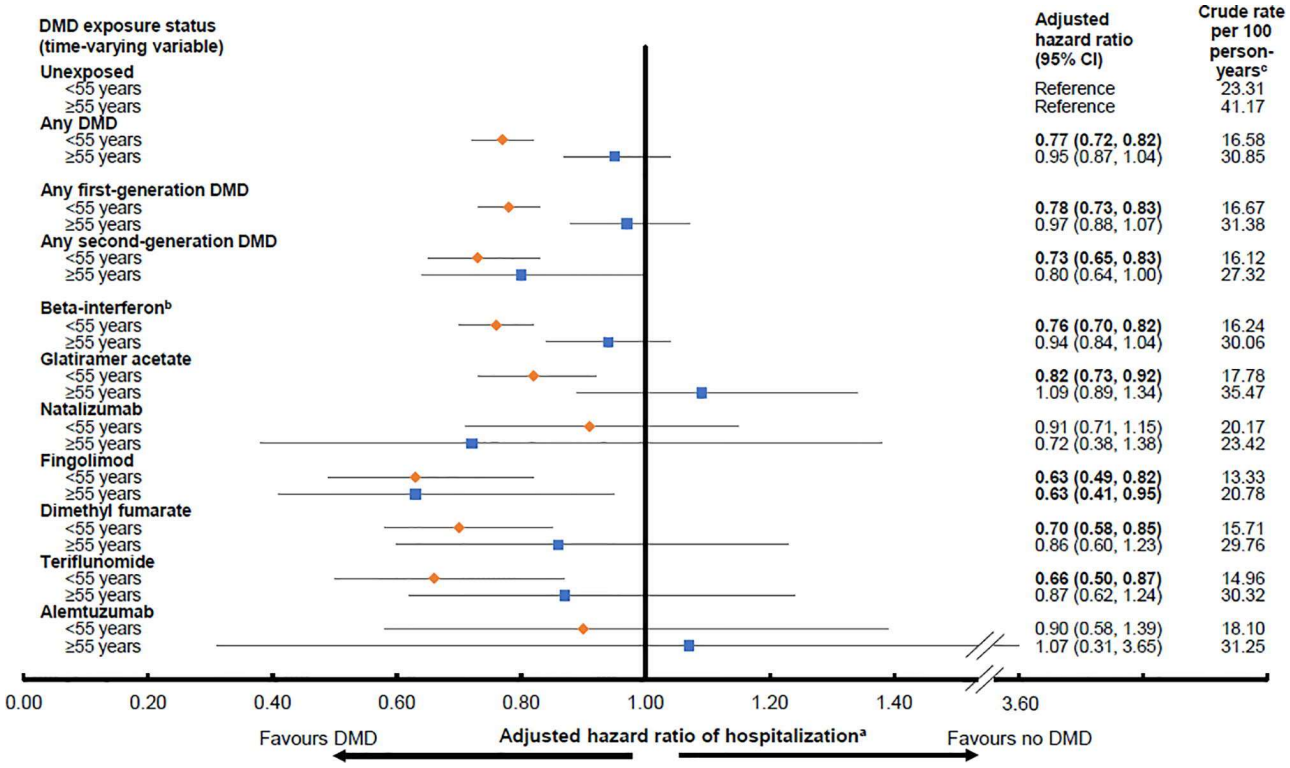

FIGURE 1 | Exposure to a disease-modifying drug for multiple sclerosis and hazard of hospitalization by age group (<55 or ≥55 years old). Key: CI, confidence interval; DMD, disease-modifying drug. Bold indicates p<0.05. [a]Results were adjusted for sex, socioeconomic status (quintiles), age (continuous) and calendar year (continuous) at the index date, and for Charlson comorbidity score (categorical: 0, 1, 2, ≥3) over time (updated on annual basis). Hazard ratios were estimated by introducing interaction terms between current age group (<55 versus ≥55 years at the time of exposure) and the DMD exposure variables shown in the Figure. [b]All beta-interferon products were grouped together as one class. [c]Person-years of follow-up for the calculation of crude rate were as per except that the duration of a hospitalization was discounted from the follow-up time.

generation DMDs, but for those aged <55 years, with beta-interferon associated with a 7% higher rate of physician visits and glatiramer acetate with an 8% lower rate. All results for the DMD exposure and physician visits analyses by age group are shown in **Figure 2**.

Complementary Analysis

By the study end 10,741 persons had ever reached their 55th birthday, with 38.4% (n=4,125/10,741) doing so by the index date and 61.6% (n=6,616/10,741) during follow-up. Approximately 15% (n=1,657/10,741) were exposed to a DMD at any time point during follow-up (**Supplementary Table 3**). While 12% (n=1,302/10,741) had their first DMD before age 55 years, nearly half of these (n=596/1,302) were no longer taking DMD once aged ≥55 years. In total, over 3% (n=355/10,741) of persons initiated their first DMD at the age of 55 years or older.

DISCUSSION

We assessed the effect of current age on the association between DMD exposure and health service utilization in a population-based MS cohort with over 200,000 person-years of follow-up, and all within a universal healthcare setting. Exposure to any DMD or to any first generation DMD (versus no DMD) was associated with a 22-23% lower hazard of hospitalization for those aged <55 years at the time of exposure, while exposure to any second generation DMD was associated with a 27% lower hazard of hospitalization. In contrast, in older adults (≥55 years), DMD exposure, whether assessed as any DMD or any first or second generation or even by individual DMDs (versus no DMD), was generally not associated with a lower risk of hospitalization. Finally, while regardless of age (<55 or ≥55 years), exposure to any DMD, relative to no DMD, was not associated with an altered rate of physician visits, considerable variation was observed across the individual DMDs. Our findings offer insights into the effects of ageing on the relationship between the DMDs used to treat MS and health services in the real-world setting.

While several studies have assessed the relationship between the MS DMDs and healthcare utilization (9–12), we were unable to find another study to compare our age-specific findings. A study from the United States co-authored by a pharmaceutical manufacturer of an MS DMD examined patterns of healthcare

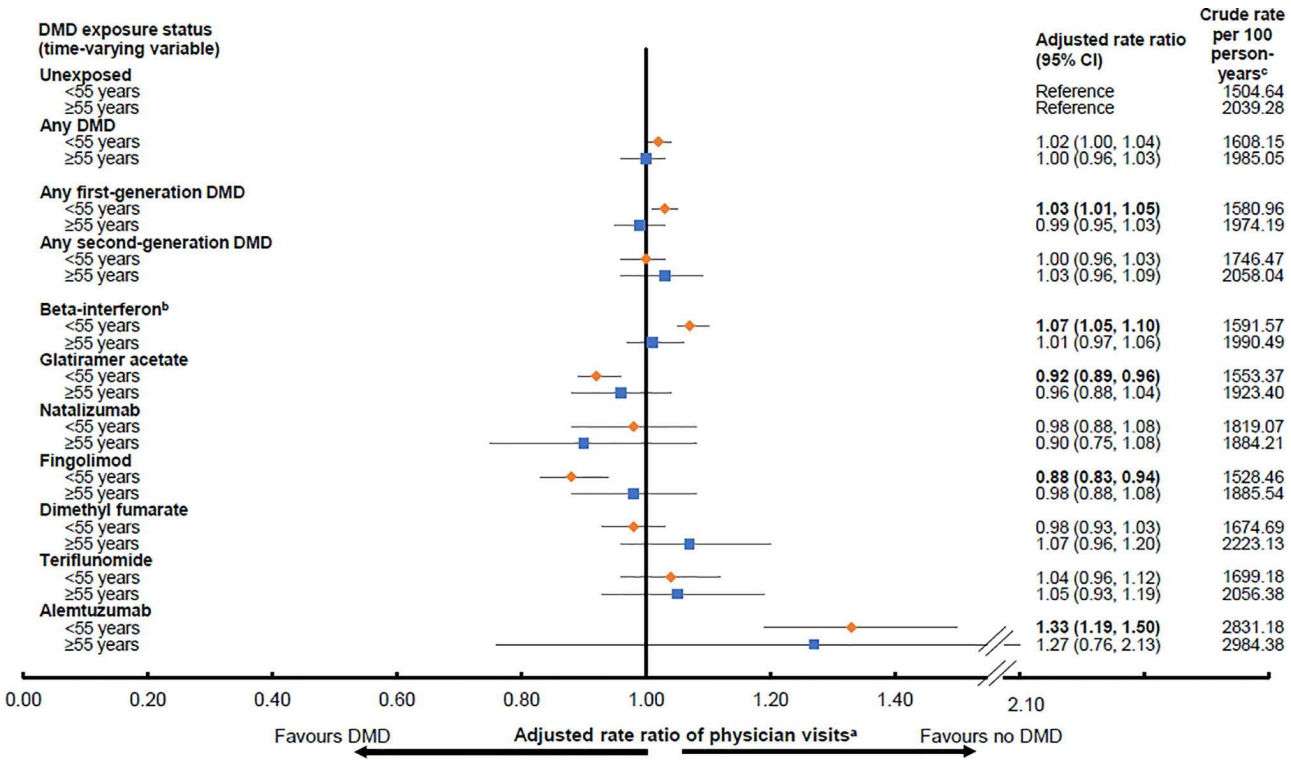

FIGURE 2 | Exposure to a disease-modifying drug for multiple sclerosis and rates of physician visits[d] by age group (<55 or ≥55 years old). Key: CI, confidence interval; DMD, disease-modifying drug. Bold indicates p<0.05. [a]Results were adjusted for sex and socioeconomic status (quintiles) at the index date, and the following characteristics over time on a yearly basis: age (continuous), calendar year (continuous), and Charlson comorbidity score (categorical: 0, 1, 2, ≥3). Rate ratios were estimated by introducing interaction terms between current age group (<55 versus ≥55 years at the time of exposure) and the DMD exposure variables shown in the Figure. [b]All beta-interferon products were grouped together as one class. [c]Person-years of follow-up are shown in **Table 2** and were used to calculate the crude rates. [d]As outlined in the study methods, neurologist visits were excluded, as were pregnancy-related visits.

utilization in 28,427 persons with MS by insurance type (commercial versus the federal insurance plan, Medicare Advantage) within different age groups (32). However, the study was cross-sectional in design, spanning just one-year and was restricted to persons under 65 years of age. The authors found that MS persons with a federal insurance plan had a significantly higher mean count of all-cause inpatient and ambulatory visits compared to those with a commercial insurance plan. While findings were consistent across age groups, at least once age 30 years was reached, the authors did not report which individual DMDs contributed to these findings (32). Efforts have also been made to examine the effects of ageing on the efficacy of DMDs by using data from clinical trials. However, there are some limitations and challenges with these studies. One example is a meta-analysis which included 26 clinical trials of 14 different DMDs published between 1995 and 2019, and comprised 28,082 relapsing-remitting MS persons. Authors found no statistically significant associations between age and reduction(s) in disease activity (measured as annualized relapse rates and magnetic resonance imaging metrics, such as gadolinium-enhancing lesions and T2 lesions) when the DMD- and placebo-treated groups were compared (33). However, as individual-level data were inaccessible, this meta-analysis had to rely on group-level average ages as reported within each clinical trial to examine potential age-related differences in DMD efficacy (33). Moreover, the original clinical trials were not designed to examine DMD efficacy in the ageing population and individuals older than 55 years were excluded from enrollment, such that the average ages of participants ranged from 33 to 40 years (33).

The differences we found in the association between DMD exposure and the hazard of hospitalizations by age group (<55 versus ≥55 years old) does concur with broader observations from both natural history studies of MS and the MS clinical trials. For example, clinical trials have demonstrated beneficial effects of DMDs on reducing or preventing MS relapses in the short-term (34), which may in turn lower the risk of hospitalization (9, 35–38). However, the frequency of MS relapses naturally decreases over time and with age (39, 40), being less common in older individuals, particularly after 60 years of age (2). Furthermore, the DMDs appear less efficacious and less effective in progressive MS (primary or secondary) (41–43) and a higher proportion of the older MS population will have progressive MS (1, 2, 39). The longer-term effects of the DMDs in preventing disability associated with disease progression and ageing is uncertain (2). For example, a study conducted in British Columbia, Canada, showed that exposure to beta-

interferon (versus no exposure) was not associated with a lower hazard of reaching an Expanded Disability Status Scale [EDSS] score of 6 in older MS adults, aged≥50 years (44). Further, a meta-analysis, which included 38 clinical trials of 13 different DMDs with over 28,000 MS persons, showed that the effects of DMDs on MS disability progression was strongly dependent on age, with limited benefits of receiving DMDs after age 53 years (5).

In our study, we found that exposure to any DMD was not associated with differences in the rate of physician visits by age group (<55 versus ≥55 years old), although variation across individual DMDs was observed, especially in the younger age group (<55 years). Use of the MS DMDs typically requires regular laboratory testing and safety-related monitoring. Therefore, it is possible that any potential benefits on, or decreases in, physician visits or hospitalizations related to an anticipated benefit of the DMDs on disease activity may be offset by the increase in safety-related monitoring (10). Higher rates of physician visits, ranging from 27-33%, were observed in both age groups (<55 and ≥55 years old at the time of exposure) while exposed to alemtuzumab, although this failed to reach significance in the older age group. Alemtuzumab requires regular monthly monitoring due to the risk of adverse events, such as autoimmune disorders, which may contribute to these higher rates (45). Similarly, exposure to beta-interferon, which requires regular monitoring for liver and thyroid function (46), was associated with a higher rate of physician visits. However, this was a much more modest 7% and only demonstrated in the younger age group (<55 years old at the time of exposure). In contrast, exposure to glatiramer acetate, which requires no formal laboratory testing (47), was associated with an 8% lower rate of physician visits, and exposure to fingolimod was associated with a 12% lower rate (again in the <55 year old age group only), despite the necessity of regular biochemical liver testing (48). Fingolimod is generally reserved as a second-line therapy in Canada, and a lower rate of physician visits may be due to decreases in disease activity.

Complementary Descriptive Analysis - DMD Use in the Older Age Group

Currently, it remains unclear if DMD treatment should be continued (or even started) in the MS population aged 55 years or older. To address this, a large phase 4 randomized controlled DMD treatment discontinuation trial is currently underway in the Unites States which includes persons ≥55 years old, and its findings may add crucial knowledge to this emerging aspect of MS care (49). While, as expected, a smaller proportion of our older (versus younger) persons with MS were DMD exposed (22, 32, 50), we also observed that the proportions of persons continuing or discontinuing DMD were similar. Specifically, the proportions of persons who initiated their first DMD before age 55 years, and who continued or discontinued once aged ≥55 years were rather similar (n=706/1,302 versus n=596/1,302, respectively) (**Supplementary Table 3**). These findings may reflect individual differences in diseases severity and/or the lack of clear treatment guidelines for the older patient population in clinical practice.

Strengths and Limitations

Our study has both strengths and limitations. Given that some of the newer second-generation DMDs only became widely available towards the end of our study, the total person-years exposed was modest for certain DMDs, particularly in the older (≥55 years) age group. Therefore, we could not examine the specific causes of hospitalizations due to modest event rates by age group which would have hindered derivation of reliable estimates. It is plausible that older individuals are at higher risk of being hospitalized for non-MS than MS-related causes (51). We cannot exclude that clinical or other characteristics that we did not have access to in our administrative data, such as MS disease course, disability level, or cognitive status, or lifestyle factors, such as smoking and alcohol consumption and/or ancestry/ethnicity may have influenced our findings. It remains possible that other confounders not available to us could also be of relevance. However, we were able to adjust for sex, socioeconomic status, and comorbidity burden over time. In addition, we were able to account for the changing treatment status of persons over time by using a longitudinal approach when examining DMD exposure. We consider the potential for selection bias in our study to be minimal given the universal healthcare setting, and our access to comprehensive health care data for all residents of the province, irrespective of ability to pay. Furthermore, we used a validated case definition in our study to select persons with MS. Other strengths of our study are the use of objectively collected population-based data, including linked health administrative information, and the long duration of follow-up (mean 11.7 years).

CONCLUSIONS

Our findings suggest that use of the DMDs to treat MS may be more effective in preventing hospitalizations in younger persons (aged <55 years), compared to older individuals (aged ≥55 years). For those aged <55 years, similar trends were observed for both the first and second generation DMDs. In contrast, a more varied and complex picture evolved when the relationship between DMD exposure and physician visits was examined in the older and younger age groups. This might, in part, reflect the different safety-related monitoring strategies required for the different DMDs. Further studies are warranted in order to expand treatment guidelines for an ageing MS population.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: As we are not the data custodians, we are not authorized to make the data available. With the appropriate approvals, the data may be accessed through the Population Data British Columbia. Requests to access these datasets should be directed to Population Data British Columbia.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the University of British Columbia's Clinical Research Ethics Board (H18-00407). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

HN, JG, and HT interpreted the results and drafted the manuscript. HN, JG, FZ, EK, CE, JF, RM, YZ, and HT conceptualized and designed the study. FZ, EK, CE, JF, RM, YZ, and HT facilitated obtaining funding (PI: Tremlett, CIHR Project and Foundation award). HN, JG, and FZ performed data analysis. All authors revised the manuscript critically for intellectual content, approved the final version to be published, and agreed to be accountable for all aspects of the work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2021.794075/full#supplementary-material

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Disease-modifying drugs, multiple sclerosis and infection-related healthcare use in British Columbia, Canada: a population-based study

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Summary

Background Much remains unknown surrounding the disease-modifying drugs (DMDs) used to treat multiple sclerosis and infection-related healthcare use in the 'real-world' setting. We examined if DMD exposure was associated with altered infection-related healthcare use.

Methods We assessed if DMD (versus no) exposure was associated with altered infection-related hospitalizations, physician claims, and prescriptions filled in British Columbia, Canada (1996–2017). Healthcare use was assessed using negative binomial and proportional means regression models, reported as sex-/age-/comorbidity-/calendar year-/socioeconomic-adjusted rate and hazard ratios [aRR, aHR], with 95% confidence intervals [CIs]).

Findings We identified 19,360 multiple sclerosis cases (13,940/19,360; 72.0% women; mean age at study start = 44.5 standard deviation, SD = 13.3; mean follow-up = 11.7 [SD = 7.3] years). Relative to unexposed periods, exposure to any DMD was associated with a lower infection-related rate of physician claims (aRR = 0.88; 95% CI:0.85–0.92) and hazard of hospitalization (aHR = 0.64; 95% CI:0.56–0.73), and a higher rate of infection-related prescriptions (aRR = 1.14; 95% CI:1.08–1.20). Exposure to any injectable or oral DMD was associated with a lower infection-related rate of physician claims (injectable aRR = 0.88; 95% CI:0.84–0.92, oral aRR = 0.83; 95% CI:0.77–0.90) and hazard of hospitalization (injectable aHR = 0.65; 95% CI:0.56–0.75, oral aHR = 0.54; 95% CI:0.38–0.77), whereas intravenous DMD exposure was not (aRR = 0.99; 95% CI:0.86–1.14, aHR = 0.73; 95% CI:0.49–1.09). Exposure to any injectable or intravenous DMD was associated with a higher rate of infection-related prescriptions (injectable aRR = 1.15; 95% CI:1.08–1.22, intravenous = 1.34; 95% CI:1.15–1.56), whereas oral DMDs were not (aRR = 0.98; 95% CI:0.91–1.05).

Interpretation DMD exposure for the treatment of MS was associated with differences in infection-related healthcare use. While infection-related hospitalizations and physician visits were lower, prescription fills were higher. How these differences in infection-related healthcare use affect outcomes in persons with multiple sclerosis warrants consideration.

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Keywords: Multiple sclerosis; Disease-modifying drugs; Infections; Healthcare use

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Research in context

Evidence before this study

Much remains unknown surrounding the disease-modifying drugs (DMDs) used to treat multiple sclerosis (MS) and infection-related healthcare use in the 'real-world' setting. Using the search terms "multiple sclerosis" and "infection", we searched for articles published through until September 2022 within PubMed.

Similar to all immunosuppressive medications, DMDs used for the treatment of MS carry risk of infections. The burden of infections in the MS population over the life span can be considerable and surpasses that seen in the general population. However, relatively few studies published to date have evaluated the role of the MS DMDs on infection risk. Evidence before this study suggests that use of any monoclonal antibody (versus any DMD) was associated with a higher incident rate of infection-related hospitalizations among MS enrollees of the Department of Defense military healthcare system (n = 8695; 2004–2017). Further, a Swedish study examined the risk of the first infection-related hospitalization in MS DMD-exposed persons only, the majority of whom (>50% of the 6421 cases) had received rituximab. Study authors were unable to access primary care information, and neither the Swedish nor US study authors examined similar MS cases not undergoing a DMD treatment.

Added value of this study

We examined the relationship between DMD exposure and infection-related healthcare use in a population-based MS cohort and explored whether any such associations were modified by characteristics such as patient age, sex, or presence of specific comorbidities. Our study added value by providing an overview of the infection-related healthcare utilization in people with MS, can help guide patient-clinician expectations surrounding infections and the DMDs as well as informing healthcare planning. Exposure to a MS DMD (versus no exposure) was associated with altered infection-related healthcare use. Interestingly, while the use of any (versus no) DMD was associated with lower infection-related hospitalizations and physician visits, prescription fills were higher. The mode of administration affected findings; while any injectable or oral DMD (versus no DMD) was associated with lower infection-related physician and hospital visits, this was less evident for the intravenous DMDs. The reasons for these differences remain subject to speculation; further investigations are warranted.

Implications of all the available evidence

Prior evidence was challenging to interpret across studies given that some study designs lacked primary care data and/or did not include MS cases not undergoing DMD treatment. All available evidence suggested that DMD exposure was associated with altered infection-related healthcare use. Also, the mode of administration affected findings. How these differences in infection-related healthcare use affect other outcomes in people with MS warrants consideration.

Introduction

In the past 25 years, a range of injectable, oral and infusion-administered disease-modifying drugs (DMDs) have been approved to treat multiple sclerosis (MS). All DMDs were approved based on relatively short-term (typically lasting 2–3 years), explanatory clinical trials, conducted in select individuals.[1] However, in routine clinical practice, a much broader range of people with MS may be expected to take DMDs for many years. Similar to all immunosuppressive medications, disease-modifying drugs used for the treatment of MS carry risk of infections.[2] Anti-infectives are therefore used by physicians in clinical practice to treat and sometimes prevent different types of infections in people with MS. The burden of infections in the MS population over the life span can be considerable and surpasses that seen in the general population.[3] A UK study found that infections represented the most common comorbidity in MS, affecting 80% of 1713 incident cases on or after MS diagnosis[4] in the primary care setting. Among the most common are the urinary tract infections[5,6] which cause an estimated 30–50% of all hospitalizations amongst MS patients.[6] Infections can trigger MS relapses and disease activity and carry a significant economic burden.[7] A 2023 US study estimated that average annual in-hospital charges for all MS inpatient hospitalizations was $US3 billion (adjusted to 2010 dollars) with infections, such as urinary tract-related, skin and soft tissue and pneumonia being major contributors.[7]

Administrative data offer the opportunity to access health-related information generated as part of routine clinical care for entire populations, and have been used to assess the infection risk in persons with MS previously.[8–11] However, relatively few studies published to date have evaluated the role of the MS DMDs on infection risk.[12–14] Of those that have, two focused on hospitalizations only,[12,14] with a (US-based study) examining just the monoclonal antibodies,[14] and a Swedish study primarily rituximab (as >50% of patients were exposed to this DMD). Finally, the third study included Canadian data but in a smaller and less contemporaneous population.[13] Further, despite the International Advisory Committee on Clinical Trials in MS call for more comorbidity-related studies,[15,16] and given the paucity of sex- and age-focused trial analyses, examining the potential impact of these characteristics on DMD outcomes in everyday clinical practice represents an unmet need. The need for age and sex-focused analyses in relation to the MS DMDs in particular has been highlighted by others[17–19]; both age and sex can

affect risk of adverse events as well as response to treatment.

We examined the relationship between DMD exposure and infection-related healthcare use in a population-based MS cohort and explored whether any such associations were modified by characteristics such as patient age, sex, or presence of specific comorbidities. We hypothesized DMD exposure will be associated with an increased use of infection-related healthcare use relative to no exposure.

Methods

Study design and data sources

Study design: observational, cohort

Our observational cohort study accessed prospectively collected population-based health administrative data in British Columbia (BC), Canada. BC has a public healthcare plan, with mandatory enrollment for residents. Encounters with the healthcare system (i.e. healthcare utilization) are routinely collected by the BC Ministry of Health, including physician and hospital visits and prescription drugs dispensed (i.e. filled) in the community or outpatient setting. Data accessed (via Population Data BC[20]) included: the Medical Services Plan[21] and Discharge Abstract Databases,[22] providing physician claims and hospital admissions/discharges-related information; PharmaNet,[23] capturing prescriptions filled at outpatient/community pharmacies; Census Geodata, providing socioeconomic status (SES), based on residential postal code linked to median neighborhood household income[24]; Registration and Premium Billing files,[25] enabling confirmation of provincial residency (via registration days within the mandatory healthcare plan) and demographics (sex, date of birth); and Vital Statistics,[26] capturing death dates.

All aforementioned data sources were complete except for SES which was missing for <1% of individuals (98 of the 19,360 MS cases). This was likely due to administrative reasons, and, therefore, we anticipate that their values to be symmetrically distributed around the median (SES = 3). The impact of the imputed values would be negligible.

Cohort selection

We used a validated algorithm to identify MS cases, requiring ≥3 MS International Classification of Diseases (ICD) codes (ICD-9/10-CA: 340/G35) from the hospital or physician data, or ≥1 prescription filled for a MS DMD (Tables 1 and 2).[27] Of note, filling a DMD prescription was not required for fulfilling this validated algorithm. This validated algorithm has been used previously,[28,29] which facilitating comparisons between studies,[29–32] and enables a population-based approach, by including all possible eligible MS cases. The algorithm has a positive predictive value (PV) of 99.5%, and the negative PV of 97.5% and has been validated against medical records and successfully applied in multiple Canadian regions.[30,33,34] The date of the first MS-specific or demyelinating disease-related ICD code (Table 1) or DMD prescription filled determined the index date. Persons with MS aged ≥18 years and resident in BC for ≥1 year pre-index date were eligible for inclusion. Based on data availability, the earliest possible index date was 1-January-1996, and all persons were followed until the earliest of emigration from BC, death, or 31-December-2017 (study end date). Our study population therefore comprised incident and prevalent MS cases. The year 1996 also represents the first full calendar year that the MS DMDs became available through the provincial government's universal health insurance plan. The vast majority of persons would not have been exposed to a DMD before the index date, aside from a very small number of persons who may have been randomized to receive a DMD as part of a clinical trial.[35]

	ICD-9	ICD-10
Multiple sclerosis		
Multiple sclerosis	340	G35
Demyelinating disease		
Optic neuritis	377.3	H46
Acute transverse myelitis	323.82 341.2	G37.3
Acute disseminated encephalomyelitis	323	G36.9
Demyelinating disease of CNS unspecified	341.9	G37.8
Other acute disseminated demyelination	not applicable	G36
Neuromyelitis optica	341.0	G36.0

ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CA = International Classification of Diseases, Tenth Revision, Canada.

Table 1: **Multiple sclerosis and demyelinating disease related codes.**

Outcomes

The three outcomes were infection-related healthcare utilization (i.e. 1. Physician claims, 2. Hospitalizations, 3. Prescriptions filled) occurring between the index date and study end date. Physician claims represented the primary outcome, and hospitalizations and prescriptions filled the secondary outcomes. Infection-related physician clams and hospitalizations were identified using ICD-9/10-CA codes (Supplementary Table S1). A wide range of infection-related codes were included as used in previous studies.[8–10] Thus, any physician visit or hospitalization resulting in an ICD code for an infection being generated as the reason for the healthcare use was considered infection-related. As anti-infectives are used to treat or prevent some types of infections, we also examined the healthcare utilization in the outpatient care settings which included prescriptions filled for antibiotics, antivirals or antimycotics. The prescriptions filled were classified using the Anatomical Therapeutic Chemical (ATC) System

Disease-modifying therapy	Drug identification number	Mode of administration	Health Canada approval date
Betaseron® (IFNB-1b)	02169649	injectable	July 1995
Extavia® (IFNB-1b)	02337819	injectable	November 2009
Avonex® (IFNB-1a)	02237770 02269201 02267594	injectable	April 1998
Rebif® (IFNB-1a)	02281708 02277492 02237317 02237319 02237320 02277492 02281708 02318253 02318261 02318288	injectable	February 1998
Plegridy® (Peg-IFNB-1a)	02444372 02444380 02444399 02444402	injectable	August 2015
Copaxone® (glatiramer acetate)	02233014 02245619 02456915 02441446 02481510	injectable	October 1997
Glatect® (glatiramer acetate)	02460661	injectable	August 2017
Tysabri® (natalizumab)	02286386	intravenous	September 2006
Gilenya® (fingolimod)	02365480 02482533	oral	March 2011
Tecfidera® (dimethyl fumarate)	02404508 02420201	oral	April 2013
Aubagio® (teriflunomide)	02416328	oral	November 2013
Lemtrada® (alemtuzumab)	02418320	intravenous	December 2013
Zinbryta® (daclizumab)	02459620 02459639	injectable	December 2016
Ocrevus® (ocrelizumab)	02467224	intravenous	August 2017

The DMDs listed represented all those available (approved) for use in MS by Health Canada at some point during the study. Daclizumab was withdrawn from the market in March 2018 due to safety concerns.

Table 2: **The disease-modifying therapies approved by Health Canada to treat multiple sclerosis (1995/6–2017): drug name (brand/generic), drug identification number, mode of administration (injectable, oral, intravenous), Health Canada approval date.**

(Supplementary Table S2).[36] Thus, any prescription filled for one of these drugs was considered 'infection-related'. To avoid double counting, physician claims with the same ICD code on the same day were considered as one claim. Similarly, any overlapping hospital stays were considered as one hospitalization, and any prescriptions filled for the same drug (i.e. same Health Canada unique drug identification number) on the same day were counted once.[29]

Exposure

The following DMDs were available/approved by Health Canada to treat MS during our study period: beta-interferon, glatiramer acetate, natalizumab, fingolimod, dimethyl fumarate, teriflunomide, alemtuzumab, daclizumab, and ocrelizumab. We identified all prescriptions filled for a DMD and determined the time each individual was exposed to that drug based on the days' supplied (via PharmaNet), allowing for a 30-day grace period.[29] Alemtuzumab and ocrelizumab exposure were defined as 12-months (alemtuzumab) and 6-months (ocrelizumab) from the date of first and any subsequent supply; if no further prescription fills occurred, a 30-day grace period was also applied. We considered a DMD as discontinued if there were no further dispensations for >90 days, or if a prescription was filled for a different DMD. For the six individuals exposed to daclizumab (withdrawn from the market for safety reasons), their follow-up was censored at the first daclizumab prescription filled.

Periods during which an individual had no DMD supply were considered 'unexposed,' and this formed the reference category. A person's DMD exposure status was examined as time-varying to account for treatment change(s) over time. Both the time period before, and after, the initiation of DMD were included in the analysis for all individuals. DMDs were grouped and assessed as any DMD, then by mode of administration

(i.e. invasiveness; injectable [beta-interferon/glatiramer acetate], intravenous [natalizumab/alemtuzumab/ocrelizumab] or oral [dimethyl fumarate/fingolimod/teriflunomide]) and finally as each individual DMD (except for ocrelizumab, as <6 cases were exposed).

Statistical analyses

We used negative binomial regression models to examine the associations between DMD exposure and infection-related physician claims and prescriptions filled, with each assessed as counts–either yearly or by DMD exposure period. The negative binomial regression is more flexible than Poisson regression since it does not require the mean and the variance of the counts to be equal. Models were fitted by generalized estimating equations (GEE) with an exchangeable working correlation matrix and person-time included as an offset.[37] Findings were reported as adjusted rate ratios (aRRs) with the corresponding 95% confidence intervals (CIs). As infection-related hospitalizations are rare, we employed a repeated time-to-event approach. The sojourn time between infection-related hospitalizations was analysed using the proportional means model for recurrent events with robust sandwich variance estimates,[38] thus allowing for multiple infection-related hospitalizations while accounting for dependence of events within an individual. Similar to the Cox proportional hazards regression model, tests for the proportional rates and means assumption are not considered necessary.[39] The hazard ratios reported represent the weighted average of the true hazard ratio over our study period. Death was treated as a censoring event. In other words, follow-up time was censored at the earliest of emigration from BC, death, or 31-December-2017 (study end date). Findings were reported as adjusted hazard ratios (aHRs) with the corresponding 95% CIs.

For the physician claims and prescriptions filled, models were adjusted for: sex and SES quintiles at the index date, and, updated annually for: age (continuous), calendar year (continuous) and comorbidities (categorized as 0, 1, 2 or ≥3). Comorbidities were measured via the Charlson Comorbidity Index, using the hospital and physician data in the one-year pre-index date and updated annually thereafter (excluding hemiplegia/paraplegia to avoid misclassifying MS complications as comorbidity[35] and hepatitis from within the liver disease comorbidity category given that this infection is an outcome variable). For hospitalizations, the same model adjustments were applied, except for age and calendar year which were measured at the index date. Statistical analyses were performed using R V.4.0.2 (R Foundation for Statistical Computing, Vienna, Austria) and SAS V.9.4 (SAS Institute, Cary, NC, USA). In a prior sample size calculation based on a time-to-event outcome,[40] we demonstrated that under a hospitalization rate of 5%, 1307 individuals with 50% DMD exposure rate would be sufficient to detect a hazard ratio of 2.0 with 80% power using a two-tailed test with a 5% probability of type I error. Our sample size has exceeded this estimation. As infection-related physician visits and prescriptions were much more common than hospitalizations, we anticipated that a smaller sample size is required to achieve the same level of power.

Complementary analyses

For physician claims only, the most common infections—those affecting the respiratory tract—were examined separately (Supplementary Table S1). For prescriptions filled, we removed the antivirals (as antivirals are commonly used prophylactically when initiating intravenous alemtuzumab) and examined this outcome using the same approach as in the main analyses. We also explored the impact of: sex, age (grouped as <45 or ≥45 years [mean age at index date]) and presence/absence of specific comorbidities on the prescription-related findings (with and without the antivirals), in relation to any DMD, and by route of DMD administration, using interaction terms. Comorbidities included two broad groups: any circulatory system disease and any mood/anxiety disorder or alcohol abuse, and then five more specific comorbidities: ischemic heart disease, hypertension, diabetes mellitus, eye/adnexa disease, and depression/anxiety (Supplementary Table S3). These were selected based on clinical relevance to MS and prevalence in the MS population, as well as potential associations with DMD use, and infection risk.[41–43] The overall burden of comorbidities was measured using Charlson Comorbidity Index that included several other comorbidities relevant to DMD use and infection risk, such as malignancy, cerebrovascular diseases, and liver and renal diseases.

Role of the funding sources

This study was supported by the Canadian Institutes of Health Research (CIHR) Project and Foundation grant (PJT-156363 and FDN-159934, PI: Tremlett). Jonas Graf received a Research Fellowship from the Deutsche Forschungsgemeinschaft (project number 438899010, GZ: GR 5665/1-1). The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

This study was part of a wider pre-registered research program (ClinicalTrials.gov; NCT04472975). We obtained ethics approval from the University of British Columbia's Clinical Research Ethics Board (H18-00407).

Results

Cohort characteristics are summarized in Table 3 (further details are available elsewhere),[35] and cohort

Characteristics	DMD treated[a], n = 4732	Not treated[a], n = 14,628	p-value
Women, n (%)	3469/4732 (73.3)	10,471/14,628 (71.6)	0.02 (Pearson's Chi-squared test)
Age at index date in years, mean (SD)	37.1 (9.8)	46 9/14,628 (13.7)	<0.0001 (Wilcoxon rank sum test)
Socioeconomic status[b], n (%)			0.65 (Pearson's Chi-squared test)
1 (lowest income quintile)	914/4732 (19 3)	2849/14,628 (19.5)	
2	870/4732 (18 4)	2825/14,628 (19.3)	
3, or unavailable	1004/4732 (21.2)	3025/14,628 (20.7)	
4	1006/4732 (21.3)	3088/14,628 (21.1)	
5 (highest income quintile)	938/4732 (19 8)	2841/14,628 (19.4)	
Comorbidity score[c], n (%)			<0.0001 (Pearson's Chi-Squared test)
0	3974/4732 (84.0)	11,077/14,628 (75.7)	
1	588/4732 (12.4)	2391/14,628 (16.4)	
2	132/4732 (2.8)	723/14,628 (4.9)	
≥3	38/4732 (0.8)	437/14,628 (3.0)	
Presence of specific comorbidities[c], n (%[d])			–
Diseases of circulatory system	677/4732 (14.3)	3368/14,628 (23.0)	
Ischemic heart disease	90/4732 (1.9)	596/14,628 (4.1)	
Hypertension	238/4732 (5.0)	1572/14,628 (10.7)	
Eye and adnexa diseases	1967/4732 (41.6)	5626/14,628 (38.5)	
Diabetes mellitus	99/4732 (2.1)	661/14,628 (4.5)	
Any mood or anxiety disorder or alcohol abuse	1415/4732 (29.9)	4348/14,628 (29.7)	
Depression and anxiety disorders	1388/4732 (29.3)	4239/14,628 (29.0)	
Follow-up[a] time in years, mean (SD)	12.0 (7.0)	11.6 (7.3)	–
Death before study end, n (%)	267/4732 (5.6)	2943/14,628 (20.1)	–
Type of DMD exposure during follow-up, n (%)[a]		NA	–
Injectable DMDs—any[e]	4124/4732 (87.2)		
Beta-interferon	3140/4732 (66.4)		
Glatiramer acetate	1719/4732 (36.3)		
Oral DMDs—any[e]	1495/4732 (31.6)		
Fingolimod	421/4732 (8.9)		
Dimethyl fumarate	758/4732 (16.0)		
Teriflunomide	520/4732 (11.0)		
Intravenous DMDs—any[e]	436/4732 (9.2)		
Natalizumab	286 (6 0)		
Alemtuzumab	179 (3 8)		
Ocrelizumab	<6		
Daclizumab[f]	6 (0 1)		
Any infection-related health service use during study period, mean (SD)	12.0 (6.99)	11.54 (7.3)	0.0001 (Wilcoxon rank sum test)

Characteristics of the multiple sclerosis study population in British Columbia, Canada (1996–2017). Details have been published previously.[34] Key: DMD, disease-modifying drugs; MS, multiple sclerosis; NA, not applicable; SD, standard deviation. The date of the first MS-specific or demyelinating disease-related event was the index date. As per data privacy and access agreements, small cell size (<6 individuals within any group) are suppressed. [a]Follow-up was from index date until the earliest of: death; emigration from the province; or study end (December 31st 2017). [b]Socioeconomic status is represented by neighborhood income quintiles (based on closest available measurement to index date). There are n = 98 unavailable SES values, likely due to administrative reasons, and, therefore, we anticipate that their values to be symmetrically distributed around the median (SES = 3). The impact of the imputed values would be negligible. [c]Comorbidities were assessed using the physician and hospital data during the one-year period prior to the index date. The comorbidity score was measured using the Charlson Comorbidity Index (modified to exclude hemiplegia/paraplegia to avoid misclassifying MS complications as comorbidity and to exclude hepatitis given that this infection is an outcome variable). [d]Some individuals had none of these comorbidities and others could have more than one, thus, the percentages are not expected to add up to 100%. Alcohol abuse was combined with mood or anxiety disorder because they both belong to the 'Mental Disorder' chapter under the ICD classification system. [e]Some people were exposed to >1 DMD; hence the sum of the individual injectable, oral or intravenous DMDs exceeds the sum of any injectable, oral or intravenous DMD. [f]As this DMD was withdrawn from the market for safety reasons, each individual's follow-up was censored at the first daclizumab prescription filled.

Table 3: **Cohort characteristics.**

creation in the Supplementary Fig. S1. Briefly, we identified 19,360 persons with MS, of whom 13,940 (72.0%) were women. The mean age (standard deviation [SD]) at index date was 44.5 (13.3) years. Overall, 4732/19,360 (24.4%) persons filled at least one MS DMD prescription, and the mean (SD) follow-up time was similar between those who did, or did not, fill a DMD prescription, with the mean being 11.7 (7.3) years for the entire group. Persons never (versus ever) filling a DMD prescription were, on average, older at the index date (46.9 [13.7] versus 37.1 [9.8] years), and had a higher comorbidity burden, while the distribution of

socioeconomic status quintiles was similar between the two groups.

Infection-related physician claims

Relative to no DMD, any DMD exposure was associated with a 12% lower rate ratio of infection-related physician claims (aRR = 0.88; 95% CI: 0.85–0.92; p < 0.0001), with similar findings for the injectable and oral DMDs, but not intravenous (aRR = 0.99; 95% CI: 0.86–1.14; p = 0.95; Fig. 1). Rate ratios were also lower for each of the individual injectable and oral DMDs, ranging from 8% lower for glatiramer acetate (p = 0.038) to 24% for teriflunomide (p < 0.0001), with dimethyl fumarate, fingolimod and beta-interferon falling in between, being 13–16% lower (aRR range: 0.76–0.92). Rate ratios did not differ for either of the intravenous DMDs (alemtuzumab aRR = 1.03, natalizumab aRR = 0.98), although the 95% CIs were wide (Fig. 1).

Infection-related hospitalizations

Relative to no DMD, any DMD exposure was associated with a 36% lower hazard of infection-related hospitalizations (aHR = 0.64; 95% CI: 0.56–0.73; p < 0.0001; Fig. 2). Lower hazards were also observed for the DMDs when examined by mode of administration, ranging from 46% for the oral DMDs (p = 0.0006), to 35% for the injectables (p < 0.0001) and 27% for intravenous, although the 95% CIs for the latter did not reach significance (aHR = 0.73; 95% CI: 0.49–1.09; p = 0.13). Somewhat similar findings were observed for the individual DMDs examined: hazards of hospitalization were significantly lower for the two injectable DMDs, glatiramer acetate (aHR = 0.61; 95% CI 0.46–0.79; p = 0.0003) and beta-interferon (aHR: 0.66; 95% CI: 0.56–0.78; p < 0.0001), and lower for the three oral DMDs, and natalizumab (aHR range: 0.45–0.66). However, only dimethyl fumarate reached statistical significance (aHR = 0.45; 95% CI: 0.27–0.75; p = 0.0027). For alemtuzumab, the 95% CI was wide in this small group, limiting interpretation (Fig. 2).

Antibiotic, antimycotic, and antiviral prescriptions

Relative to no DMD, any DMD exposure was associated with a 14% higher rate ratio of infection-related prescription fills (aRR = 1.14; 95% CI: 1.08–1.20; p < 0.0001; Fig. 3). Significantly higher rate ratios were also observed for the injectable DMDs (aRR = 1.15; 95% CI: 1.08–1.22; p < 0.0001) as well as the intravenous DMDs (aRR = 1.34; 95% CI: 1.15–1.56; p = 0.0001). However, we did not observe a higher rate ratio of infection-related prescription fills for the oral DMDs (aRR = 0.98; 95% CI: 0.91–1.05; p = 0.62). By individual DMD, rate ratios were higher, by 12% for beta-interferon (p = 0.0017), 23% for glatiramer acetate (p < 0.0001), and 126% for alemtuzumab (p < 0.0001), but not natalizumab (p = 0.45) or the three oral DMDs.

Complementary analyses

The distributions of infection-related healthcare utilization are included within Supplementary Table S4.

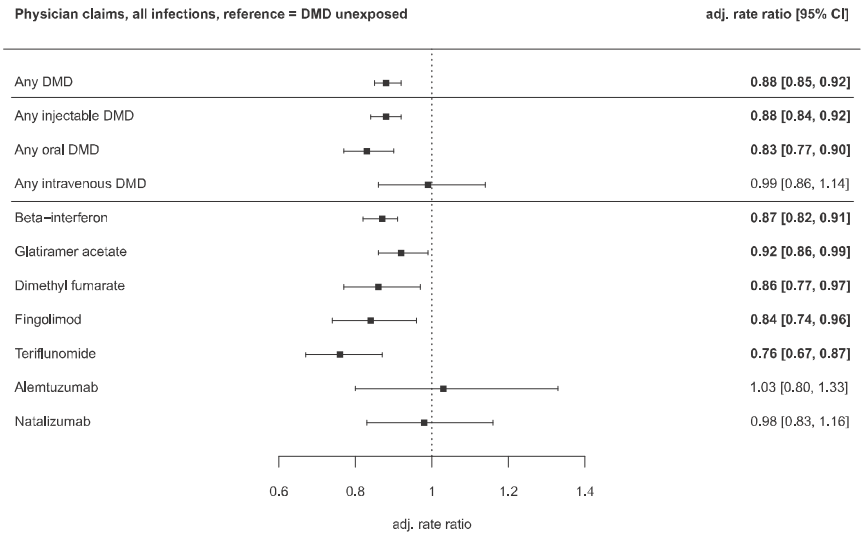

Fig. 1: Infection-related physician claims in the multiple sclerosis study population[a] in British Columbia, Canada (1996–2017) expressed as adjusted rate ratios. Key: DMD, disease-modifying drugs; adj., adjusted; CI, confidence interval; bold depicts statistical significance. a Follow-up was from index date until the earliest of: death; emigration from the province; or study end (December 31st 2017). Rate ratios were adjusted for the following covariates: sex, socioeconomic status (categorical; quintiles) at the index date, and, updated annually, age (continuous), calendar year (continuous) and comorbidities (categorized as 0, 1, 2 or ≥3 comorbidities) measured using the Charlson Comorbidity Index.

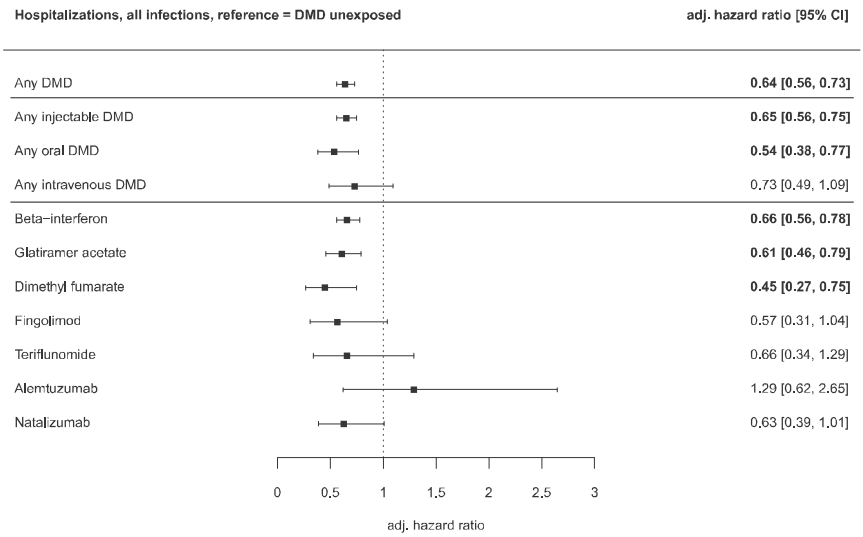

Fig. 2: Infection-related hospitalizations in the multiple sclerosis study population[a] in British Columbia, Canada (1996–2017) expressed as adjusted hazard ratios. Key: DMD, disease-modifying drugs; adj., adjusted; CI, confidence interval; bold depicts statistical significance. a Follow-up was from index date until the earliest of: death; emigration from the province; or study end (December 31st 2017). Hazard ratios were adjusted for the following covariates: sex, comorbidity score (0, 1, 2 or ≥3; updated annually) measured using the Charlson Comorbidity Index, and the following covariates at the index date: age (continuous), socioeconomic status (categorical; quintiles), and calendar year (continuous).

Any, versus no DMD exposure was associated with a 9% lower rate of respiratory tract infection-related physician claims (aRR = 0.91; 95% CI: 0.87–0.96; p = 0.0007), with similar findings for the injectable/oral DMDs (aRR = 0.90 [p = 0.0004]/0.87 [p = 0.029]), Fig. 4. In contrast, any intravenous DMD was associated with a 22% higher rate (aRR = 1.22; 95% CI: 1.01-1.48; p = 0.037). For the individual injectable and oral DMDs, only beta-interferon was associated with a significantly lower rate ratio (aRR = 0.89; 95% CI: 0.84–0.95; p = 0.0003). While rate ratios were higher for alemtuzumab (aRR = 1.42; 95% CI: 0.90–2.23; p = 0.12) and natalizumab (aRR = 1.16; 95% CI: 0.95–1.42; p = 0.14), the 95% CIs were wide and neither reached significance.

When the antivirals were removed from the prescriptions filled, the direction of findings remained largely the same, except for the intravenous DMDs, which no longer differed versus no DMD exposure (p = 0.90; Fig. 5). Further, while a higher rate ratio was still observed for alemtuzumab (aRR = 1.11; p = 0.34), this no longer reached significance. For the prescriptions filled for any anti-infective, sex, but not age affected findings (Supplementary Table S5). In detail, among women, any DMD exposure (versus none) was associated with a 18% higher rate of infection-related prescription fills (aRR = 1.18; p < 0.0001); this differed significantly from that found among men (aRR = 0.98; p = 0.82). A similarly higher rate ratio among women (aRR = 1.20; p < 0.0001) than among men (aRR = 0.99; p = 0.91) was observed for the injectable DMDs. For the comorbidities, rate ratios of anti-infective prescriptions filled were similar regardless of whether that comorbidity was present or not, except for the intravenous DMDs only, where it was lower when depression/anxiety was present (Supplementary Table S5). However, after removing the antivirals, this latter finding was no longer significant (data not shown).

Discussion

In this population-based study, we examined the relationship between DMD exposure and infection-related healthcare encounters in a large MS cohort by accessing more than 20-years of prospectively collected data, which comprised information on all hospital and physician visits, and prescriptions filled. Our study provided an overview of the infection-related healthcare utilization in people with MS to inform healthcare planning. Exposure to a MS DMD (versus no exposure) was associated with altered infection-related healthcare use. Interestingly, while the use of any (versus no) DMD was associated with lower infection-related hospitalizations and physician visits, prescription fills were higher. The mode of administration affected findings; while any injectable or oral DMD (versus no DMD) was associated with lower infection-related physician and hospital visits, this was less evident for the intravenous DMDs. Further, while the injectable and intravenous DMDs were associated with a 15–34% higher rate (aRR) of infection-related prescription fills, no measurable effect was observed for the latter when the antivirals were

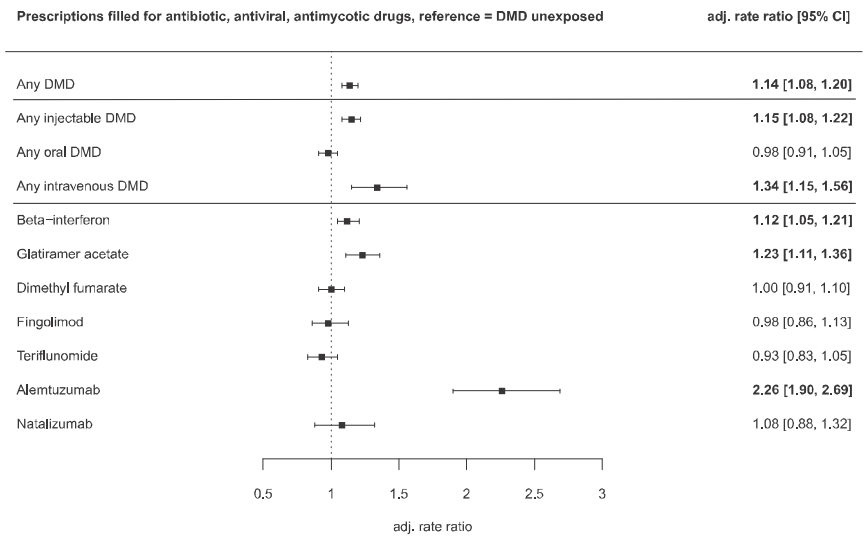

Fig. 3: Infection-related prescriptions filled by the multiple sclerosis study population[a] in British Columbia, Canada (1996–2017) expressed as adjusted rate ratios. Key: DMD, disease-modifying drugs; adj., adjusted; CI, confidence interval; bold depicts statistical significance. a Follow-up was from index date until the earliest of: death; emigration from the province; or study end (December 31st 2017). Rate ratios were adjusted for the following covariates: sex, socioeconomic status (categorical; quintiles) at the index date, and, updated annually, age (continuous), calendar year (continuous) and comorbidities (categorized as 0, 1, 2 or ≥3 comorbidities) measured using the Charlson Comorbidity Index.

removed. The reasons for these differences remain subject to speculation; further investigations are warranted. In contrast, the oral DMDs had no measurable effect on infection-related prescription fills, whether or not the antivirals were included. Also, if the mode of administration itself may alter the infection risk remains uncertain. How these differences in infection-related healthcare use affect other outcomes in people

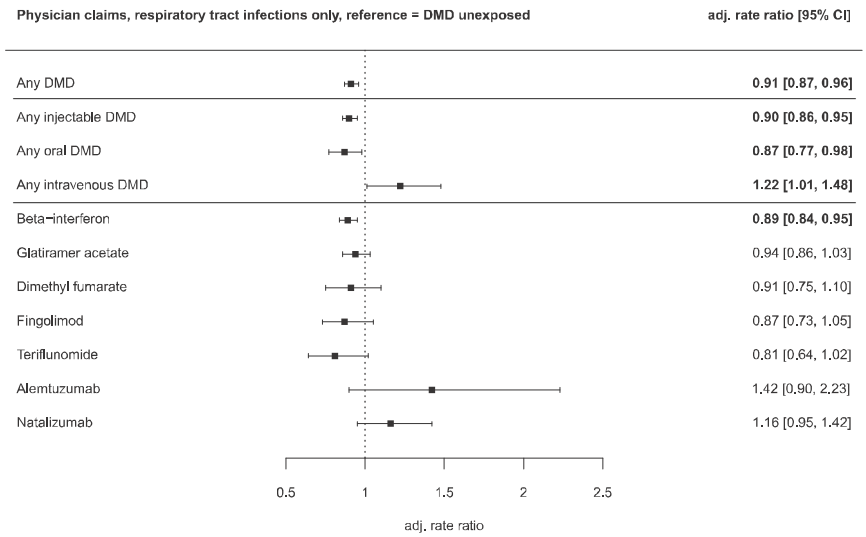

Fig. 4: Association between disease-modifying drug (DMD) exposure and respiratory tract infection-related physician claims in the multiple sclerosis study population[a] in British Columbia, Canada (1996–2017) expressed as rate ratios. Key: DMD, disease-modifying drugs; adj., adjusted; CI, confidence interval; bold, 95% CI did not include 1. ICD-9-codes used to identify respiratory tract infection physician claims: 460, 461, 462, 463, 464, 465, 466, 473, 474, 476, 480, 481, 482, 483, 484, 485, 486, 487, 490. a Follow-up was from index date until the earliest of: death; emigration from the province; or study end (December 31st 2017). Rate ratios were adjusted for the following covariates: sex, socioeconomic status (categorical; quintiles) at the index date, and, updated annually, age (continuous), calendar year and comorbidities (categorized as 0, 1, 2 or ≥3 comorbidities) measured using the Charlson Comorbidity Index.

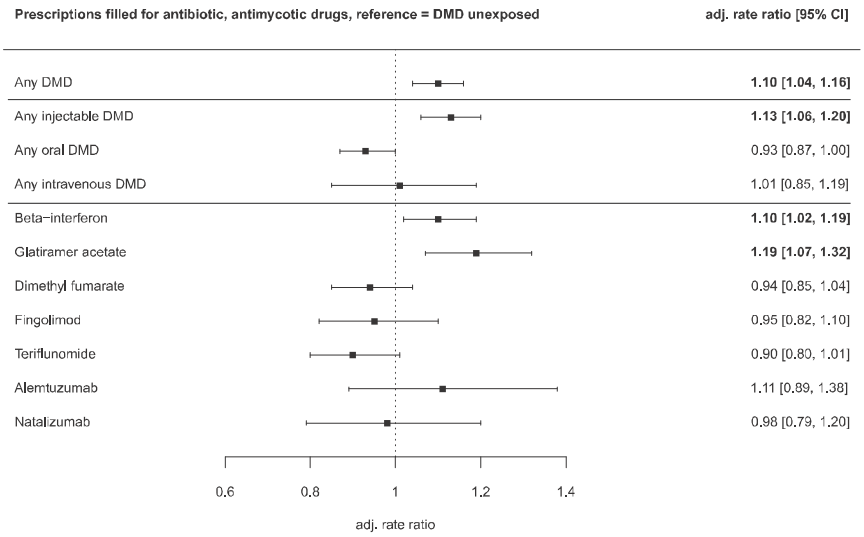

Fig. 5: Association between disease-modifying drug (DMD) exposure and antibiotic or antimycotic prescriptions filled only in the multiple sclerosis study population[a] in British Columbia, Canada (1996–2017) expressed as rate ratios. Key: DMD, disease-modifying drugs; adj., adjusted; CI, confidence interval; bold, 95% CI did not include 1. Prescriptions filled for antivirals (bold in Supplementary Table S2) were not considered as outcome. a Follow-up was from index date until the earliest of: death; emigration from the province; or study end (December 31st 2017). Rate ratios were adjusted for the following covariates: sex, socioeconomic status (categorical; quintiles) at the index date, and, updated annually, age (continuous), calendar year and comorbidities (categorized as 0, 1, 2 or ≥3 comorbidities) measured using the Charlson Comorbidity Index.

with MS warrants consideration. Future studies may also wish to consider the contribution of other medications a person with MS may be taking (with or without a DMD) and their possible contribution to infection risk.

Few other studies have assessed the relationship between DMD use and infections in the MS population. A prior study from our group, also using data from British Columbia (1996–2013, n = 6793), observed lower infection-related hospitalization risk in those exposed to the newer DMDs available at that time. However, findings did not reach statistical significance in this smaller cohort, and all the oral and intravenous DMDs were grouped together due to their lower uptake at that time.[13] Our current study advanced these findings considerably by accessing more contemporary data and a much larger MS population (n = 19,360) with a longer follow-up period.[13] A US study found that use of any monoclonal antibody (versus any DMD) was associated with a higher incident rate of infection-related hospitalizations among MS enrollees of the Department of Defense military healthcare system (n = 8695; 2004–2017).[14] However, the individual DMDs used were not specified. Finally, a Swedish study examined the risk of the first infection-related hospitalization in MS DMD-exposed persons only, the majority of whom (>50% of the 6421 cases) had received rituximab.[12] Study authors were unable to access primary care information, and neither the Swedish nor US study authors examined similar MS cases not undergoing a DMD treatment, making it challenging to compare across studies.[12,14] Our study further advances current understanding of infection risk in MS as we were also able to examine respiratory tract infection-related physician claims by route of DMD administration, and observed that the intravenous DMDs were associated with a higher rate (by 22%) versus no DMD. This increase in infections likely relates to drug-induced immune cell depletion or cell trafficking disruptions. Also consistent with our observation, the most commonly reported infections in MS persons enrolled in a clinical trial or drug company initiated observational study, and treated with an intravenous DMD (alemtuzumab or natalizumab), were respiratory-related.[44,45]

Ours is one of few studies to assess infection-related prescriptions filled in the MS population, comparing periods of DMD exposure versus no exposure. While a previous smaller study from British Columbia found that MS cases (n = 7179; 1996–2013) had a higher risk to fill an infection-related prescription relative to the general population (aRR = 1.57; 95% CI: 1.49–1.65), that study was not designed to examine associations with the MS DMDs.[8] Our current findings suggested that relative to no DMD use, injectable DMDs were associated with a 12–23% higher rate (aRR) of filling an infection-related prescription, while the oral DMDs, or the intravenously administrated natalizumab were not. Further, the direction of these findings persisted whether antivirals were included or not. These results warrant further investigation. It is possible that use of one of these DMDs increases the likelihood that a clinician would

recommend an anti-infective drug (relative to a patient not being treated with a DMD). This in turn could lower the risk of an infection-related hospitalization or physician visit. However, for the intravenously administered alemtuzumab, while we observed a 126% higher rate of infection-related prescription fills, this was attenuated after removal of the antivirals, resulting in only an 11% higher rate which no longer reached significance. Although the wide 95% CIs for this finding create uncertainty, the observed difference in rate ratios of infection-related prescription fills may reflect prophylactic use of antivirals when initiating alemtuzumab.

Our findings further underscore the importance of considering sex-based disparities in healthcare to reduce the sex differences in health outcomes. We found that sex, but not age affected findings; consistent with the absence of age-related increases in DMD-associated infections in pooled information from 45 clinical trials.[46] For sex, we specifically observed that DMD exposed (relative to unexposed) women with MS had a higher rate (aRR) of filling infection-related prescriptions and that such increase was not observed in men with MS. While a systematic review of sex-differences in primary care found that in the general population, women were more likely than men to be prescribed an antibiotic,[47] we were unable to find another study to directly compare our findings. This dearth of sex-specific studies in relation to the effects of the MS DMDs has been highlighted by others.[17] Our findings further underscore the importance of considering sex-based differences/disparities in healthcare.

We were also able to examine the influence of comorbidities on the relationship between DMD exposure and infections. Of the select comorbidities studied, absence (versus presence) of depression/anxiety disorders was associated with a higher rate of anti-infective prescription fill in relation to use of an intravenous DMD. However, this association was not present after removing the antivirals, which are recommended for prophylactic use when receiving alemtuzumab. Despite the International Advisory Committee on Clinical Trials in MS call for further work in this area,[15,16] we were unable to find other studies with which to compare our findings. Thus, our findings underscore the needs for further examinations of the potential impacts of comorbidities on outcomes related to the DMDs used in everyday clinical practice.

Strengths and limitations

Study strengths included access to comprehensive, prospectively collected population-based health administrative data, minimizing selection or recall bias. Our cohort also included over 4700 DMD treated MS cases, totaling 24,967 8 person-years of exposure. Nonetheless, our ability to examine infection-related healthcare associated with more recently approved DMDs, that only became available towards the end of our study, was rather limited. Moreover, as more DMDs with different mechanisms of action become available, future studies may benefit from using different approaches to grouping the DMDs when evaluating infection-risk as the mode of administration may not always reflect the underlying infection-related risk associated with that drug. We also did not have access to data related to ethnicity, and whilst we could examine the route of administration (delivery), for the injectables, we did not differentiate between the two main modes of delivery–subcutaneous and intramuscular, or consider the drug dose used and medication adherence. While access to population-based healthcare data was a study strength, we were unable to independently verify the accuracy of each diagnosis with an infectious disorder specialist. We acknowledge the general limitation of administrative data; they are captured for billing purposes and health system management–not clinical purposes–thus may be subject to misclassification. We did not have access to clinical data (other than that available in the health administrative and billing data), such as the MS disease course, severity or activity, or disability measures such as the Expanded Disability Status Scale (EDSS) score, or relevant demographic data such as education (e.g. highest degree) and lifestyle-related information (e.g. smoking or alcohol consumption). Still, we were able to adjust for sex, age, socioeconomic status, and comorbidity burden measured using the Charlson Comorbidity Index. It would be of value for future studies to consider other comorbidities (e.g. autoimmune disease) which were not captured by this study. We cannot exclude residual bias in our findings. Furthermore, we accounted for the changing DMD treatment status over time, thus avoiding immortal time bias, a major threat in pharmaco-epidemiological studies.[48–50] We aimed to compare the infection risk of DMD exposed versus unexposed MS cases; it would be of value for future, appropriately designed studies to consider comparing the infection risk between each individual DMD.

Conclusion

To the best of our knowledge, this is the largest, population-based study to examine the relationship between the MS DMDs and infection-related healthcare use. While use of any DMD was not associated with an increased risk of infection-related hospitalizations or rate of physician visits, prescription fills for an anti-infective agent were higher. However, both the route of DMD administration and sex of the person with MS affected these findings. How the differences in infection-related healthcare use identified affect other outcomes in persons with MS warrants further study.

Contributors

Jonas Graf, and Helen Tremlett interpreted the results and drafted the manuscript.

Jonas Graf, Huah Shin Ng, Feng Zhu, José M A Wijnands, Charity Evans, John D. Fisk, Ruth Ann Marrie, Yinshan Zhao, and Helen Tremlett conceptualized and designed the study.

Jonas Graf (Research Fellowship from the Deutsche Forschungsgemeinschaft), as well as Feng Zhu, Charity Evans, John D. Fisk, Ruth Ann Marrie, Yinshan Zhao, and Helen Tremlett facilitated obtaining funding (PI: Tremlett, CIHR Project and Foundation award).

Jonas Graf, Huah Shin Ng, and Feng Zhu accessed the data and performed data analysis.

All authors revised the manuscript critically for intellectual content, approved the final version to be published, and agreed to be accountable for all aspects of the work.

Data sharing statement

As we are not the data custodians, we are not authorized to make the data available. With the appropriate approvals, the data may be accessed through the Population Data British Columbia.

Declaration of interests

Jonas Graf has received in the last 3 years travel/meeting/accommodation reimbursements from Merck Serono, Sanofi-Genzyme, Grifols, and a Research Fellowship from the Deutsche Forschungsgemeinschaft (project number 438899010, GZ: GR 5665/1-1).

Huah Shin Ng has received funding from the MS Society of Canada's endMS Postdoctoral Fellowship, and the Michael Smith Foundation for Health Research Trainee Award.

Feng Zhu, Yinshan Zhao, José M A Wijnands, and Charity Evans declare no conflicts.

John Fisk receives research funding from CIHR, the MS Society of Canada, Crohn's and Colitis Canada, Research Nova Scotia, the Nova Scotia Health Authority Research Fund, and licensing and distribution fees from MAPI Research Trust.

Ruth Ann Marrie receives research funding from: CIHR, Research Manitoba, MS Canada, Multiple Sclerosis Scientific Foundation, Crohn's and Colitis Canada, National Multiple Sclerosis Society, CMSC, the US Department of Defense, the Arthritis Society, Biogen Idec (no funds to her/her institution) and Roche (no funds to her/her institution), and is supported by the Waugh Family Chair in Multiple Sclerosis.

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Disclaimer: Access to data provided by the Data Steward(s) is subject to approval, but can be requested for research projects through the Data Steward(s) or their designated service providers. All inferences, opinions, and conclusions drawn in this manuscript are those of the authors, and do not reflect the opinions or policies of the Data Steward(s).

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lana.2023.100667.

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MULTIPLE SCLEROSIS JOURNAL | MSJ

Short Report

Emergency department use by persons with MS: A population-based descriptive study with a focus on infection-related visits

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Jonas Graf, Huah Shin Ng, Feng Zhu, Yinshan Zhao, José MA Wijnands, Charity Evans, John D Fisk, Ruth Ann Marrie and Helen Tremlett

Abstract: We described emergency department (ED) visits (all visits and infection-related) by persons with multiple sclerosis (MS) in British Columbia, Canada (1 April 2012 to 31 December 2017). We identified 15,350 MS cases using health administrative data; 73.4% were women, averaging 51.4 years at study entry. Over 4.9 years of follow-up (mean), 56.0% of MS cases visited an ED (mean = 0.6 visits/person/year; total = 37,072 visits). A diagnosis was documented for 25,698 (69.3%) ED visits, and 18.4% (4725/25,698) were infection-related. Inpatient admissions were reported for 20.4% (5238/25,698) of all and 29.2% (1380/4725) of infection-related ED visits. Findings suggest that the ED plays a substantial role in MS healthcare and infection management.

Keywords: Multiple sclerosis, emergency department, healthcare utilization, population-based data

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Introduction

Emergency department (ED) presentations represent an important aspect of health care utilization in the general population.[1,2] Compared to the general population, persons with multiple sclerosis (MS) frequently access the healthcare system, with infections contributing to this higher healthcare use. For example, persons with MS had 41% more infection-related physician claims (adjusted rate ratio = 1.41; 95% confidence interval: 1.36–1.47) versus a sex-, age-, and region-matched non-MS population.[3] However, relatively little is known about ED utilization by persons with MS.[4–6] Here, we described overall and infection-related ED use in an MS population.

Methods

We performed a descriptive, population-based study in British Columbia (BC), Canada, using linked health administrative data (via Population Data BC[7]), including Medical Service Plan Billing Information[8] (providing physician claims); the Discharge Abstract Database[9] (providing hospital admissions/discharges); PharmaNet[10] (for prescriptions filled at outpatient/community pharmacies); Census Geodata (providing socioeconomic status estimates); Registration and Premium Billing files[11] (providing BC residency status via the mandatory healthcare plan registration days); Vital Statistics[12] (capturing death dates); and the National Ambulatory Care Reporting System dataset[13] (providing ED-related visit dates and Diagnosis Shortlist codes,[14] including infections; Supplementary Table 1) starting 1 April 2012).

All MS cases were identified with a validated algorithm.[15] Study entry date was the later of the first MS/demyelinating disease-related International Classification of Diseases (ICD-9/10) code, or first disease-modifying drug (DMD) prescription filled, or 1 April 2012 (start of the ED date). All included persons were ⩾18 years old and BC residents for ⩾1 year pre-study entry; follow-up ended at the earliest of death, emigration, or 31 December 2017. Comorbidities were measured using a modified Charlson Comorbidity Index during the 1-year pre-study entry.[16–18] MS cases ever filling a DMD prescription during follow-up were described.

Results

We identified 15,350 MS cases (11,270 (73.4%) women; Table 1), of whom 86.5% (13,274/15,350) entered the study in 2012/2013, as per data availability. At study entry, the mean age was 51.4 years (standard deviation (SD) = 13.8), and 26.5% (4072/15,350) had ⩾1 comorbidity. During the mean 4.9

Table 1. Characteristics of the multiple sclerosis study population in British Columbia, Canada (2012–2017).

Characteristics at the index date	Total, $n=15,350$
Sex, *n* (%)	
Women	11,270 (73.4)
Men	4080 (26.6)
Age at study entry in years	
Mean (SD)	51.4 (13.8)
Age group at study entry, *n* (%)	
<30 years	1017 (6.6)
30–39 years	2137 (13.9)
40–49 years	3495 (22.8)
50–59 years	4339 (28.3)
⩾60 years	4362 (28.4)
Calendar year at study entry,[a] *n* (%)	
2012–2013	13,274 (86.5)
2014–2015	1203 (7.8)
2016–2017	873 (5.7)
Socioeconomic status,[b] *n* (%)	
1 (lowest income quintile)	2903 (18.9)
2	2905 (18.9)
3	3048 (19.9)
4	3302 (21.5)
5 (highest income quintile)	3043 (19.8)
Unavailable	149 (1.0)
Comorbidity score,[c] *n* (%)	
0	11,278 (73.5)
1	2497 (16.3)
2	990 (6.4)
⩾3	585 (3.8)
Characteristics over the study follow-up	
Follow-up[a] time in years	
Mean (SD)	4.9 (1.6)
Filled ⩾1 DMD prescription at any time during follow-up,[d] *n* (%)	3079 (20.3)
• *First-generation DMD—any*	*2190/3079 (71.1)*
• *Second generation DMD—any*	*1716/3079 (55.7)*
Visits to the ED, no. of persons with MS (%)	
Never	6747 (43.9)
Once only	2849 (18.6)
Twice only	1690 (11.0)
⩾3 times[e]	4064 (26.5)
Total number of ED visits	37,072
Mode of transportation, *n* (%)[e]	
No ambulance	26,359 (71.1)
Ground ambulance only	10,691 (28.8)
Air ambulance only	15 (<0.1)
Combination of air and ground ambulance	7 (<0.1)
Triage level received, *n* (%)[e]	
Resuscitation	294 (0.8)
Emergent	6145 (16.6)
Urgent	18,689 (50.4)
Semi-urgent	10,340 (27.9)
Non-urgent	1378 (3.7)
Unknown	226 (0.6)

DMD: disease-modifying drugs; N/A: not applicable; SD: standard deviation; ED: emergency department.
[a]Follow-up was from study entry to end. As per data availability, the earliest possible study entry was 1 April 2012.
[b]Socioeconomic status is represented by neighborhood income quintiles, based on the closest available measurement to the study entry date.
[c]Comorbidity was measured using the Charlson Comorbidity Index (modified to exclude hemiplegia/paraplegia to avoid misclassifying MS complications) during the 1-year period prior to the study entry date.[17,18] The proportion of persons with MS scoring 1 or more on the Comorbidity Index is consistent with prior work[16] conducted in similar cohorts. The most common comorbid conditions (present at study entry) which were identified using the Index were "chronic pulmonary disease" (present in 1102/15,350; 7.2% of the study cohort), "diabetes mellitus without chronic complications" (1011; 6.6%), and "cerebrovascular disease" (629; 4.1%).
[d]Captured as prescriptions filled; some people were exposed to >1 DMD during follow-up; hence, the sum of cases filling first- and second-generation DMD prescriptions exceeded the sum of cases ever filling a DMD prescription; first-generation DMDs included beta-interferon and glatiramer acetate, and second-generation DMDs included natalizumab, fingolimod, dimethyl fumarate, teriflunomide, alemtuzumab, daclizumab, and ocrelizumab. Pre-study entry (1 January 1996 to 31 March 2012) 19.5% (2991/15,350) of MS cases had ever filled a DMD prescription.
[e]The denominator used to estimate the following proportions was the total number of ED visits captured during follow-up ($n=37,072$); some people had more than one ED visit during follow-up; hence, the sums of ED visits exceed the total number of persons with at least one ED visit.

(SD=1.6) years of follow-up, 56.0% (8603/15,350) of MS cases visited an ED, totaling 37,072 visits; 15,350 MS cases averaged 0.6 (SD=1.6) visits/person/year. MS cases visiting an ED at least once during follow-up ($n=8603$) with (vs without) comorbidity at study entry were older (mean age=56.5 (SD=14.3) vs 49.5 (SD=13.7) years) and averaged more ED visits/person/year (1.3 (SD=2.4) vs 0.9 (SD=1.9)). More than a quarter of MS cases had ⩾3 ED visits (4064/15,350; 26.5); of these 1383 (34.0%) of 4064 had ⩾1 comorbidity at study entry. Most ED visits by MS cases did not require an ambulance (26,359/37,072; 71.1%); 28.8% required a ground ambulance (10,691/37,072) and >95% were of semi-urgent or higher priority (35,468/37,072).

ED visits with a known diagnosis

Diagnostic codes were reported for 69.3% (25,698/37,072) of ED visits (summarized in Supplementary Table 2). These visits were made by 74.2% (6384/8603) of MS ED users. Of these, the most frequent primary diagnoses were "abdominal pain/colic" (1279/25,698 visits; 5.0%), "urinary tract infection" (1277 visits; 5.0%), and "MS" (1225 visits; 4.8%). When combined, 18.4% (4725/25,698) of ED visits were infection-related with 32.2% (2056/6384) of MS participants having at least one such visit. Nearly one-third (1380/4725; 29.2%) of infection-related ED visits led to hospitalization, while 20.4% (5238/25,698) of all ED visits made by 27.9% (2404/8603) of cases did so (Supplementary Tables 2 and 3).

DMD users versus non-users

Persons who filled ⩾1 DMD prescription(s) during follow-up ("DMD users") were younger at study entry date than non-users (mean age = 41.9 (SD = 11.1) vs 53.8 (SD = 13.3) years). However, the proportions accessing an ED at least once were generally similar (1806/3079, 58.0% of DMD users and 6797/12,271, 55.6% of non-user), as was the study follow-up time (4.8 years (SD = 1.6) for DMD users vs 4.9 (SD = 1.6) for non-users).

Socioeconomic status

There were no clear patterns across the socioeconomic quintiles at study entry for the MS cases: ever/never filling a DMD prescription during follow-up, ever/never being hospitalized subsequent to an ED visit, or for the five most common ED diagnoses (data not shown).

Conclusion

Over 50% of persons with MS had more than one ED consultation during our nearly 6-year observation period; one-quarter visited an ED three or more times. Nearly 20% of ED visits were infection-related; one-third resulted in hospitalization, whereas one-fifth of all-cause ED visits did so. MS cases with ⩾1 (vs without) comorbidity at study entry averaged more ED visits/person/year. Our intentionally descriptive study has several limitations. While the overall burden of infection-related ED visits was considerable in our MS population, this could be higher as diagnoses were unavailable for one-third of all ED visits. Furthermore, our study lacked MS-specific clinical information, such as relapses, and a comparison to the general population. Our 1-year pre-study look-back period may have reduced the detection of comorbidities. Strengths of our study included the large cohort of MS cases identified using a validated algorithm within a geographically defined population with universal healthcare coverage, including ED visits. Our results suggest that the ED visits by MS cases often lead to hospitalizations, perhaps more so for infection-related visits. Further studies are necessary to better understand the importance of ED use by persons with MS.

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Supplemental material

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Letters

RESEARCH LETTER

Updated Multiple Sclerosis Incidence, 2015-2022

Multiple sclerosis (MS) prevalence has risen globally, increasing 30% since 2013 to 2.8 million individuals affected in 2020.[1] In contrast, a paucity of information on MS incidence exists.[2] While females are twice as likely to develop MS than males, whether the incidence sex ratio has changed over time is unclear. We evaluated current MS incidence by sex in Germany.

Supplemental content

Methods | This cohort study used nationwide, pseudonymized outpatient claims data covering approximately 87% of the German population to assess MS incidence for 2015 to 2022. The claims data contain information on persons living in Germany, covered by statutory health insurance (SHI), and having at least 1 SHI-accredited physician claim in the respective calendar year. Ethical approval and informed consent are not required for claims data studies according to the German Code of Social Law. We followed the STROBE reporting guideline.

We accessed demographic data (age, sex) and SHI-accredited physician diagnoses based on *ICD-10, German Modification* codes and diagnostic certainty (ie, assured, suspected, status post, excluded). Multiple sclerosis incidence was assessed in SHI-insured patients with at least 4 years of claims data and at least 1 any-cause outpatient SHI-accredited physician visit in 1 of the reporting calendar years of interest and in the third year before the reporting calendar year (ie, 3-year preobservation period). For children born in the preobservation period or reporting calendar year, at least 1 any-cause outpatient visit in the birth year and 1 in the reporting calendar year were sufficient for inclusion.

Cases of MS were identified using a validated algorithm[3] requiring at least 3 MS-specific (*ICD-10, German Modification* code G35) physician claims. Patients were considered to have incident MS if they received an MS diagnosis and the diagnostic modifier of assured in 1 quarter and at least 2 of 3 consecutive quarters thereafter (≥3 MS-specific claims within a case-specific period of 4 consecutive quarters) without any demyelinating or MS disease claims (eTable in Supplement 1) during the 3-year preobservation period. This approach ensures the same MS case definition for each reporting calendar year, including 2022. Annual crude and age- and sex-standardized (against the 2021 German population) cumulative incidence (incident cases divided by at-risk population) were calculated. Statistical analyses were performed using SAS, version 9.4 (SAS Institute Inc).

Results | The SHI-covered at-risk population with at least 4 years of observation time grew from 59 686 090 (2015) to 63 282 052 (2022) people (**Table**). The annual number of incident MS cases ranged from 9507 (2019) to 10 633 (2021), with a stable female predominance ranging from 67.6% (2020) to 71.1% (2016) (vs 28.9% [2016] to 32.4% [2020] in males). Median patient age also remained stable across calendar years. Between 2015 and 2022, the age- and sex-standardized cumulative MS incidence per 100 000 people declined marginally and varied between 15.65 (95% CI, 15.34-15.97) in 2019 and 17.46 (95% CI, 17.12-17.80) in 2016 (**Figure**; Table). The highest cumulative MS incidence was observed for patients aged 25 to 34 years (Figure).

Discussion | This cohort study shows that among more than 60 million people covered by universal health care in Germany, the number of incident MS cases has remained stable. However, in line with assumptions made in a review

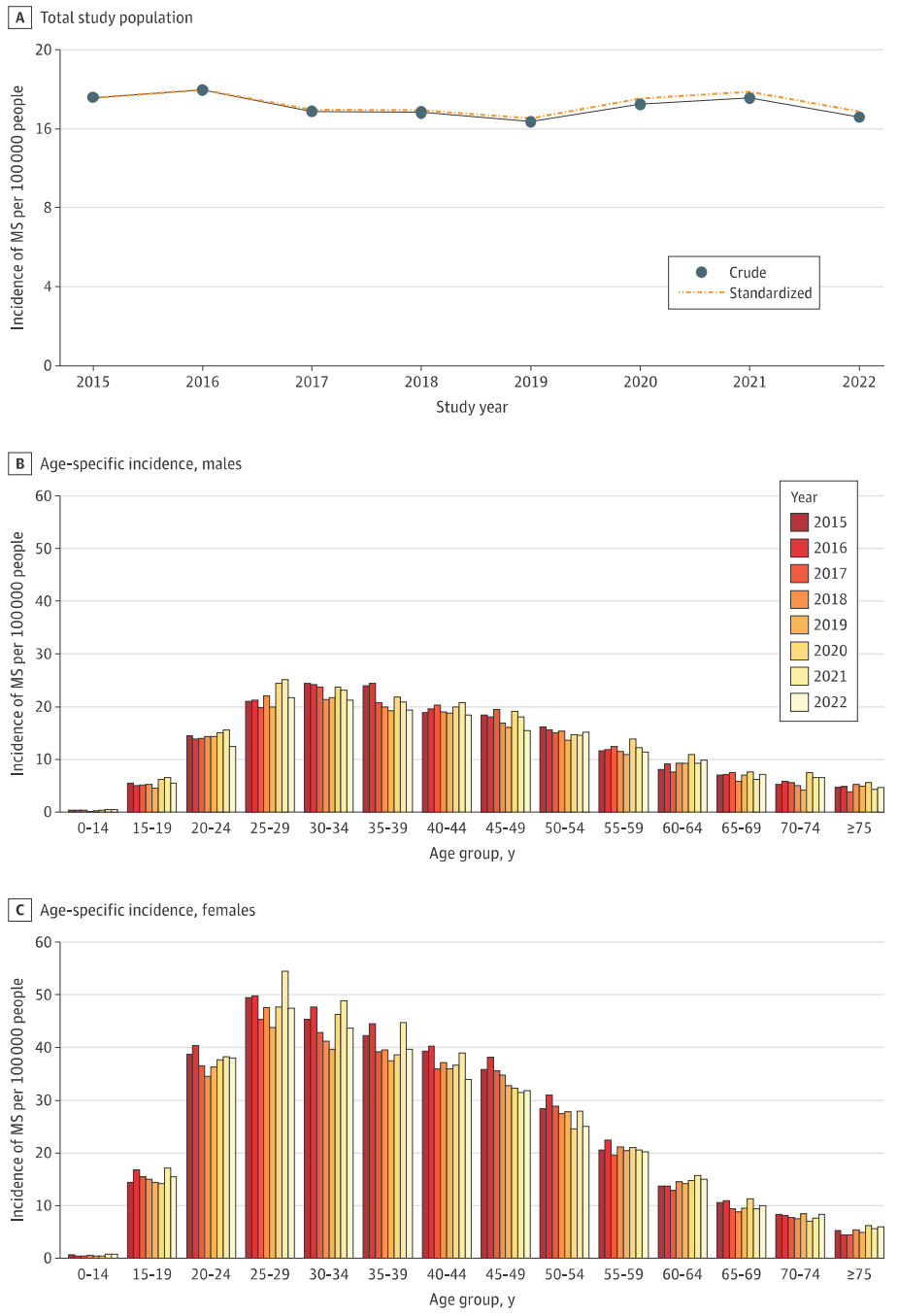
Table. Cumulative Incidence of MS per 100 000 People and Demographics of Patients Covered by Statutory Health Insurance in Germany, 2015-2022[a]

Calendar year	2015	2016	2017	2018	2019	2020	2021	2022
Crude cumulative incidence (95% CI)	16.99 (16.66-17.32)	17.45 (17.12-17.78)	16.09 (15.77-16.41)	16.04 (15.72-16.36)	15.45 (15.14-15.76)	16.54 (16.22-16.87)	16.94 (16.62-17.26)	15.73 (15.43-16.04)
Age- and sex-standardized cumulative incidence (95% CI)	16.97 (16.63-17.3)	17.46 (17.12-17.8)	16.2 (15.88-16.53)	16.18 (15.86-16.5)	15.65 (15.34-15.97)	16.92 (16.59-17.25)	17.32 (16.99-17.66)	16.09 (15.78-16.41)
No. of patients with incident MS	10 139	10 563	9760	9813	9507	10 198	10 633	9957
Age, y[b]								
Median (IQR)	42 (30-53)	42 (30-52)	42 (30-53)	42 (30-53)	42 (31-54)	41 (30-55)	40 (30-53)	41 (30-55)
Mean (SD)	42.7 (15.6)	42.6 (15.4)	42.7 (15.4)	43.2 (15.8)	43.3 (15.8)	43.5 (16.5)	42.5 (15.9)	43.3 (16.2)
Sex, No. (%)								
Female	7187 (70.9)	7515 (71.1)	6809 (69.8)	6866 (70.0)	6651 (70.0)	6898 (67.6)	7382 (69.4)	6886 (69.2)
Male	2952 (29.1)	3048 (28.9)	2951 (30.2)	2947 (30.0)	2856 (30.0)	3300 (32.4)	3251 (30.6)	3071 (30.8)

[a] At-risk population covered by statutory health insurance and at least 4 years of observation time in Germany: 2015, 59 686 090; 2016, 60 527 652; 2017, 60 641 448; 2018, 61 171 280; 2019, 61 550 441; 2020, 61 638 432; 2021, 62 776 324; 2022, 63 282 052.

[b] At December 31 of the calendar year of interest.

Figure. Annual Cumulative Incidence of Multiple Sclerosis (MS) in Germany, 2015-2022



study,[4] the cumulative incidence per 100 000 people declined slightly over the short study period, which may have been influenced by a growing population or immigration[5] and a shortened lag time of diagnosis driven by updated diagnostic criteria with a higher sensitivity.[6] Similar to other regional estimates, we found a stable sex ratio, with females approximately twice as likely to develop MS as males.[1,2] Trend variations between studies may be influenced by different case ascertainment methods and/or longer observation periods.[4] Although a limitation of our study is that some older cases of MS may have been misclassified as incident, our main finding of a constant number of incident cases of MS may inform health care planning.

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Concept and design: Graf, Akmatov, Tremlett, Holstiege.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Graf.
Critical review of the manuscript for important intellectual content: All authors.
Statistical analysis: Graf, Akmatov, Holstiege.
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ORIGINAL COMMUNICATION

Misdiagnoses and delay of diagnoses in Moyamoya angiopathy—a large Caucasian case series

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Abstract

Background The lacking awareness of healthcare providers bears the risk of delayed or false diagnoses in rare diseases. No systematic data about misdiagnoses of Moyamoya angiopathy (MMA) are available.

Objective To evaluate the rate and pattern of missed diagnoses in MMA.

Methods Retrospective analysis of a consecutive case series from a single German referral center. Rates of missed or delayed diagnoses in Caucasian MMA patients were calculated based on discharge letters from other hospitals and systematic chart review.

Results Out of 192 Caucasian patients eventually diagnosed with MMA at our center, an initial misdiagnosis was identified in 119 patients (62%). The time between onset and diagnosis was 1 year in 24 patients, 2 years in 23 patients, 3 years in 10 patients, and > 3 years in 49 patients (mean 5.28, median 3, standard deviation 5.11, and range 4–26 years). The most common misdiagnoses were cerebral vasculitis (31%), etiologically ill-defined stroke diagnoses (30.2%), and MS (3.6%).

Conclusions This is the first systematic report which shows that patients with MMA are at high risk to be falsely diagnosed and treated. Depiction of typical vascular abnormalities in angiopathy is essential. Normal CSF cell counts, negative oligoclonal bands, and lack of infratentorial lesions as well as gadolinium-positive T1 lesions on MRI may be red flags differentiating this vasculopathy from vasculitis and MS.

Keywords Moyamoya · Misdiagnosis · Vasculitis · Multiple sclerosis

Introduction

Moyamoya angiopathy (MMA) is a rare non-inflammatory arteriopathy with stenosis or occlusion of intracranial part of internal carotid artery as well proximal parts of anterior and middle cerebral artery [1]. MMA is more common in Asia, and epidemiological data outside Asia are not clear [1–3]. Young patients present with hemodynamic or embolic transient or manifest ischemic events, with cerebral bleedings and a wide range of other cerebral symptoms including cognitive dysfunction [4, 5].

The etiology of MMA is still unknown [6, 7]. While there is a common association with autoimmune thyroid disorders and a link to HLA haplotypes, evidence for an immune mediated attack on vessels underlying the disease is not strong and immunosuppressive therapy is not effective. The current double-hit hypothesis [7], nonetheless, considers a role of immunologic triggers in the context of genetic predisposition [8]. Case reports have illustrated that MMA may mimic very common diseases like multiple sclerosis (MS) [9–11], but also other rare conditions including primary central nervous system vasculitis (PCNSV) [12] and leptomeningeal metastases [13, 14]. In MMA, it is crucial to make a correct and early diagnosis especially in the light

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of possible negative treatment consequences [15]. Patients with MMA are at a high risk of not being recognized early, before debilitating complications have set in, and of being misdiagnosed and wrongly treated. Surgical bypass interventions can minimize the high risk for recurrent ischemic and hemorrhagic complications [16, 17] (recently showed also in Caucasians [18, 19]), and antiplatelet therapy can reduce embolic strokes [20]. Misdiagnosis of MMA as a PCNSV [12, 21] or MS can result in inappropriate treatments carrying the potential risk to significantly harm the patient. However, systematic studies about the rate of misdiagnoses in MMA are lacking, particularly in regions outside Asia. Real-world evidence describing the frequency of misdiagnoses in MMA is warranted.

Materials and methods

Drawing on data from longstanding adult consecutive cohorts [3, 12, 22–24], we conducted a monocentric retrospective chart review study at the Department of Neurology of the Alfried Krupp Hospital in the metropolitan Rhine-Ruhr area in western Germany from 2010 to 2018. The chart review was performed by an ICD-10 search for ICD-10 I67.5. Included were all Caucasian patients meeting all diagnostic criteria of the Research Committee of the Japanese Ministry of Health and Welfare for Moyamoya disease and Moyamoya syndrome (umbrella term: MMA) [6, 25]. In addition, patients with unilateral arteriopathy were included if detailed assessment (see below) indicated a unilateral variant of Moyamoya angiopathy. All diagnoses were based on specialized assessments by the endauthor (MK) taking into account medical history, clinical examination, MRI, conventional angiography, serum and CSF laboratory studies and exclusion of differential diagnoses [26]. Patients with non-Caucasian ethnical background were excluded from study participation. Demographic data, age at disease onset, age at diagnosis, records cardiovascular risk factors and inflammatory markers were analyzed. Discharge letters from outside hospitals were reviewed for the previous diagnoses. Misdiagnoses were classified according to clinical, neuroradiological and laboratory data into the categories "stroke-like", "unspecific" or "others", as illustrated in Fig. 1.

The time between onset of first symptoms and correct diagnosis was assessed by retrospective chart review. Time intervals until establishment of the correct diagnosis were summarized in complete years (< 1 years, 1–2 years, 2–3 years, and so on). Statistical comparisons were made using one-way analysis of variance for multiple comparisons with Bonferroni post-hoc test. Statistical analysis and graphs were completed with Prism 6 (Graph Pad, La Holla, CA).

All relevant data are provided in this manuscript. The study was approved by the ethics committee of the University of Duisburg-Essen (registration number 13-5496-BO). Due to retrospective character of the study, and in line with the approval, no patient´s consent was necessary. There is no study registration number.

Results

Demographic data

During 2010 to 2018, 192 patients were diagnosed with MMA (ICD-10 I67.5) in our referral center for rare stroke entities and met the above-mentioned inclusion/exclusion criteria. Of these, 144 (75%) were female and 48 (25%) were male. The patients were diagnosed with bilateral Moyamoya disease ($n = 140$, 72.9%), unilateral variant of Moyamoya disease ($n = 47$, 24.5%), bilateral Moyamoya syndrome ($n = 3$, 1.6%), and unilateral variant of Moyamoya syndrome ($n = 2$, 1%). The mean age of symptom onset was 32.7 years (range 1–64; the age of disease onset was unknown in 2 patients). Mean age at diagnosis was 35.1 years (range 3–67; unknown in 3 patients). Furthermore, 25 (13%) patients were children (age < 18) at disease onset. Of these, 19 (76%) received at least one misdiagnosis. An overview of the demographic data is provided in Table 1.

Delay of diagnosis

Since this study was performed retrospectively, it was only possible to determine the latency between symptom onset and correct diagnosis based on age at first symptoms and age at correct diagnosis in 187 patients: The diagnosis was delayed 1 year or longer in 106 patients (56.7% of 187 patients). The time between onset and diagnosis was 1 year in 24 patients (22.6%), 2 years in 23 patients (21.7%), 3 years in 10 patients (9.4%), and > 3 years in 49 patients (46.2%) (mean 5.28, median 3, standard deviation 5.11, range 4–26 years). Delay of correct diagnosis did not differ between stroke-like, vasculitis, MS, or unspecific misdiagnoses (one-way ANOVA, multiple comparisons, Bonferroni correction; Fig. 2).

Misdiagnoses

119 patients (62.0%) received at least one misdiagnosis before the correct diagnosis was made (total of 126 misdiagnoses; missing data in 1 patient): 45 patients were misdiagnosed with an inflammatory, 36 patients with a stroke-like, and 45 patients with another disorder. An unspecific misdiagnosis was made in 28 cases (62.2% of patients misdiagnosed with another disorder, compare Fig. 1). An instant correct diagnosis was made in 73 patients (38%). An overview of the recruitment is provided in Fig. 1 and of the

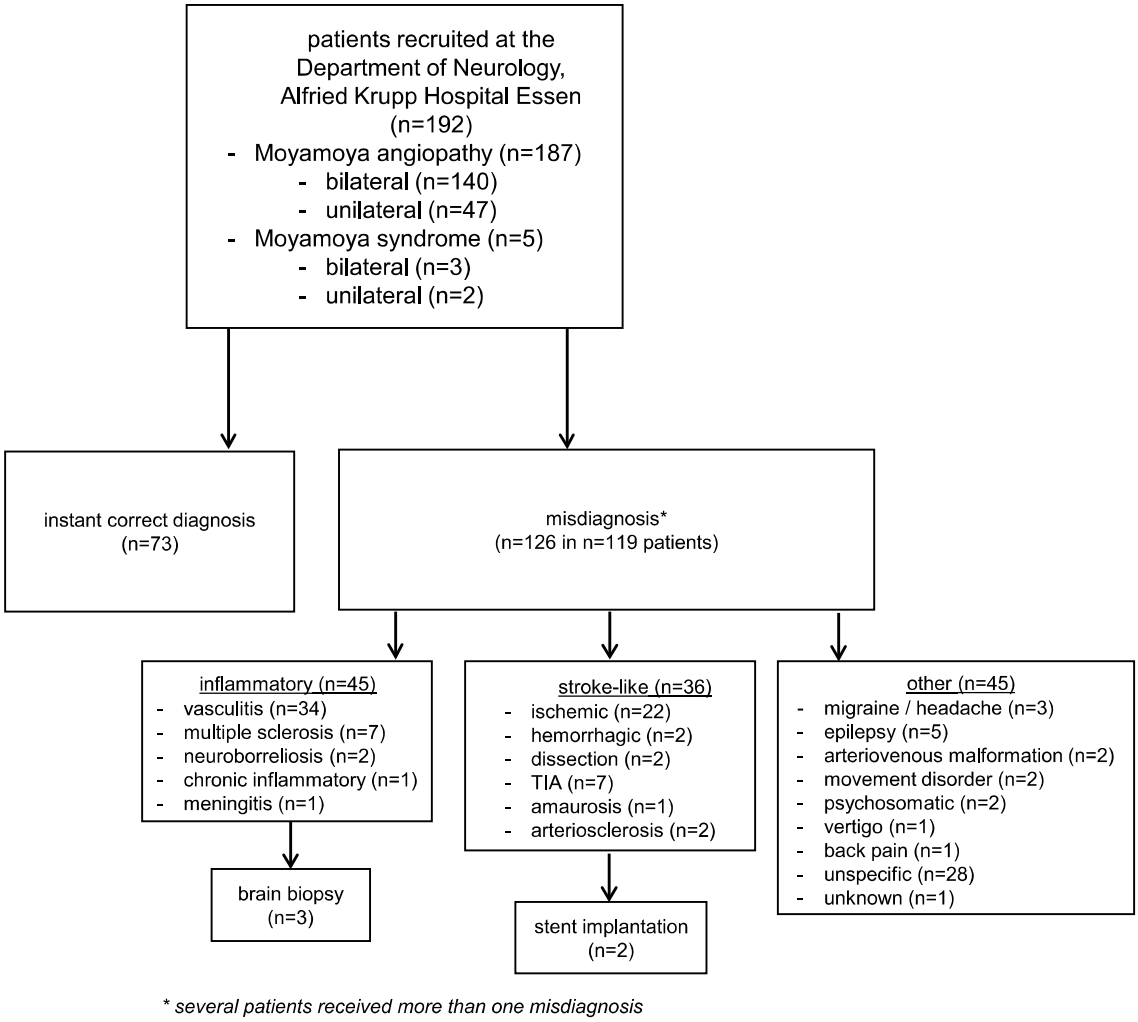

Fig. 1 Recruitment. Flowchart of the subject recruitment at the Department of Neurology, Alfried Krupp Hospital Essen. *TIA* transient ischemic attack

Table 1 Overview of the demographic data of our Moyamoya angiopathy patient cohort

Total ($n=192$)	Correct diagnosis ($n=73$)	Misdiagnosis ($n=119$)
Male	17 (23%)	31 (26%)
Female	56 (77%)	88 (74%)
Unilateral	20 (27%)	28 (24%)
Bilateral	53 (73%)	91 (76%)
Age of onset	33.5 years	31.9 years
Age of diagnosis	33.5 years	36.6 years

patients' characteristics in Table 2. CSF oligoclonal bands were negative in all patients but one, who was misdiagnosed with MS.

Misdiagnosis of MMA had an effect on diagnostic work-up and therapy. Among the patients misdiagnosed

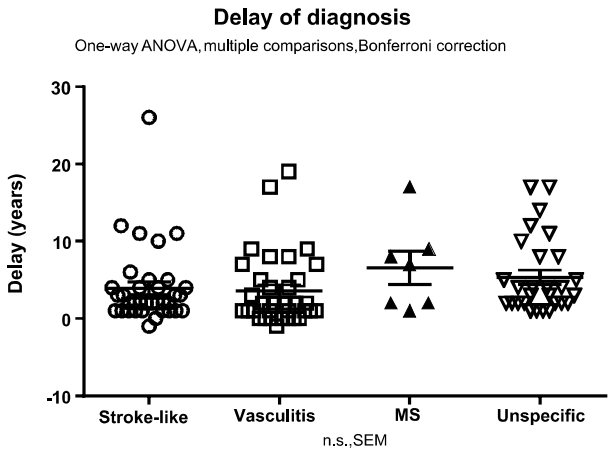

Fig. 2 Variance analysis of the delay of diagnosis. *MS* multiple sclerosis, *n.s.* not significant, *SEM* standard error of the mean

Table 2 Overview of patients' characteristics

Misdiagnosis	Mean age at correct diagnosis	Delay of diagnosis	CVRF positive			Inflammatory markers positive		
	in years	in years	aHTN	Smoking	Adiposity	OCB	ANA	ANCA
Total ($n=119$, m.d. 1)	36.62 m.d. 1	4.64 md. 2	59 (50.9%) m.d. 2	49 (43.4%) m.d. 5	30 (26.1%) m.d. 3	4 (4.5%) m.d. 29	9 (10.9%) m.d. 36	1 (1.2%) m.d. 36
Stroke-like ($n=36$)	38.31 m.d. 1	3.94 m.d. 1	24 (68.6%) m.d. 1	18 (51.4%) m.d. 1	13 (37.1%) m.d. 1	0 m.d. 11	1 (4.2%) m.d. 12	0 m.d. 12
Vasculitis ($n=34$)	36.97 md. 0	3.59 m.d. 0	16 (47.1%) m.d. 0	12 (36.4%) m.d. 1	12 (36.4%) m.d. 1	2 (5.9%) m.d. 0	4 (11.8%) m.d. 0	1 (2.9%) m.d. 0
Multiple sclerosis ($n=7$)	33.71 m.d. 0	6.57 m.d. 0	4 (57.1%) m.d. 0	3 (50%) m.d. 1	2 (28.6%) m.d. 0	1 (14.3%) m.d. 0	0 m.d. 0	0 m.d. 0
Inflammatory, other ($n=4$)	36 m.d. 0	6.75 m.d. 0	3 (75%) m.d. 0	2 (50%) m.d. 0	3 (75%) m.d. 0	0 m.d. 1	0 m.d. 2	0 m.d. 2
Unspecific ($n=28$)	34.29 m.d. 0	5.36 m.d. 0	12 (44.4%) m.d. 1	13 (48.1%) m.d. 1	3 (10.7%) m.d. 0	2 (10%) m.d. 8	4 (16.7%) m.d. 4	0 m.d. 8
Epilepsy ($n=5$)	36.8 m.d. 0	7.8 m.d. 0	1 (20%) m.d. 0	1 (20%) m.d. 0	2 (40%) m.d. 0	0 m.d. 2	0 m.d. 4	0 m.d. 4
Headache ($n=3$)	30.67 m.d. 0	10 m.d. 1	2 (66.7%) m.d. 0	1 (33.3%) m.d. 0	0 m.d. 0	0 m.d. 1	0 m.d. 2	0 m.d. 2
Other ($n=9$)	40.88 m.d. 1	6.5 m.d. 1	4 (44.4%) m.d. 0	1 (12.5%) m.d. 1	0 m.d. 1	0 m.d. 4	0 m.d. 4	0 m.d. 4
Correct diagnosis ($n=73$)	33.54 m.d. 1	n/a	36 (49.3%) m.d. 0	24 (34.3%) m.d. 3	22 (30.6%) m.d. 1	2 (3.7%) m.d. 19	6 (11.1%) m.d. 19	0 m.d. 19

CVRF cardiovascular risk factors, *aHTN* arterial hypertension, *OCB* oligoclonal bands, *ANA* antinuclear antibodies, *ANCA* anti-neutrophil cytoplasmic antibodies, *n/a* not applicable, *m.d.* missing data

for vasculitis, three underwent brain biopsy in the diagnostic process, six received steroids and two received cyclophosphamide.

Discussion

The major new findings of our study are the very high rate of misdiagnoses and the long delay of correct diagnoses in MMA. This is the first systematic report which shows that patients with MMA are at high risk to be falsely diagnosed and treated.

Inflammatory disorders were the most common misdiagnoses in our MMA cohort. It is interesting that MMA was misdiagnosed not only as frequent diagnoses like MS, but also as other rare diagnoses like CNS vasculitis. It is noteworthy that misinterpreting the ischemic MMA lesions as indicative of MS [27] or the stenoses as vasculitis may be harmful for patients regarding the diagnostic (brain biopsy) or therapeutic (steroid/cyclophosphamide treatment in vasculitis) approach [12, 21, 28]. Treatment because of a misdiagnosis as vasculitis not only bears the risks of steroid side effects like Cushing syndrome or diabetes but also the risk for precipitating disabling strokes or hemorrhages resulting from MMA pathology (see Fig. 3) [12]. In our cohort, patients misdiagnosed as MS were treated with harmless but expensive injectable therapies (glatiramer acetate and interferon beta) for years. However, nowadays, misdiagnosis as MS could be more dangerous, since the therapeutic approach in MS considered nonresponsive to platform drugs includes aggressive treatments with potentially serious adverse effects [29–31]. In our cohort, CSF markers such as oligoclonal bands were normal in all but one patient misdiagnosed as MS. Since the 2017 revision of the McDonald diagnostic criteria for MS, oligoclonal bands now have a more important role than before [32]. Therefore, the absence of oligoclonal bands should be considered a red flag concerning the diagnosis of MS and should lead to diagnostic re-consideration. Moreover, Kelly et al. showed that atypical symptoms as headaches—which are often in MMA [23]—as well as atypical MRI features are red flags for non-demyelinating diseases [33] (Fig. 4).

Distribution of lesions on brain imaging contributes to differential diagnosis between MMA and CNS inflammatory disorders [33]. None of the seven patients misdiagnosed as MS in our series had lesions in the corpus callosum. In contrast to MS, MMA does not cause infratentorial and spinal cord lesions, because almost exclusively, the territories of the anterior and middle cerebral arteries are affected. In addition, gadolinium-enhancing T1 lesions are very infrequent in MMA. Ultimately, assessment of young patients with recurrent neurological symptoms

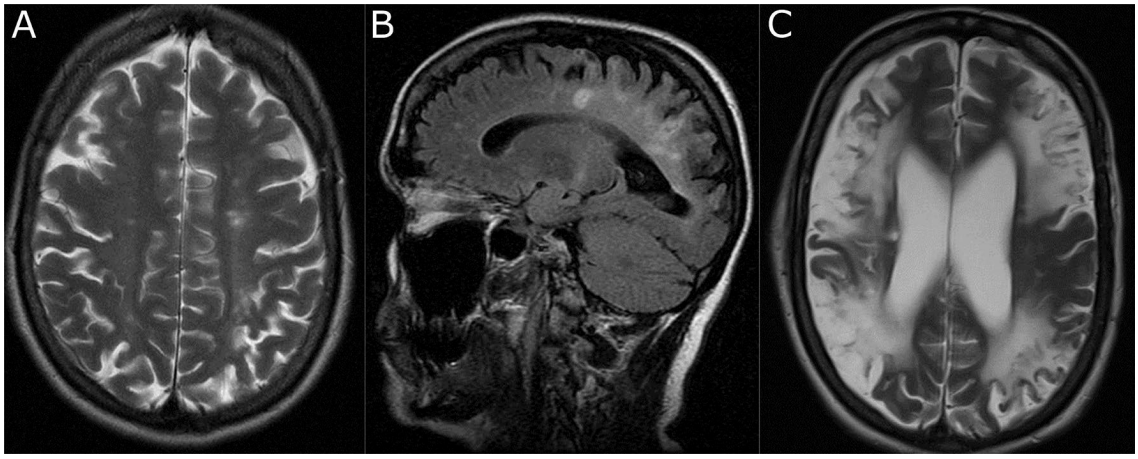

Fig. 3 MRI of a 30 year-old female patient in 2008 **a, b** misdiagnosed as MS despite negative oligoclonal banding in CSF and treated with beta interferons for years. **c** The MRI after recurrent strokes in 2014

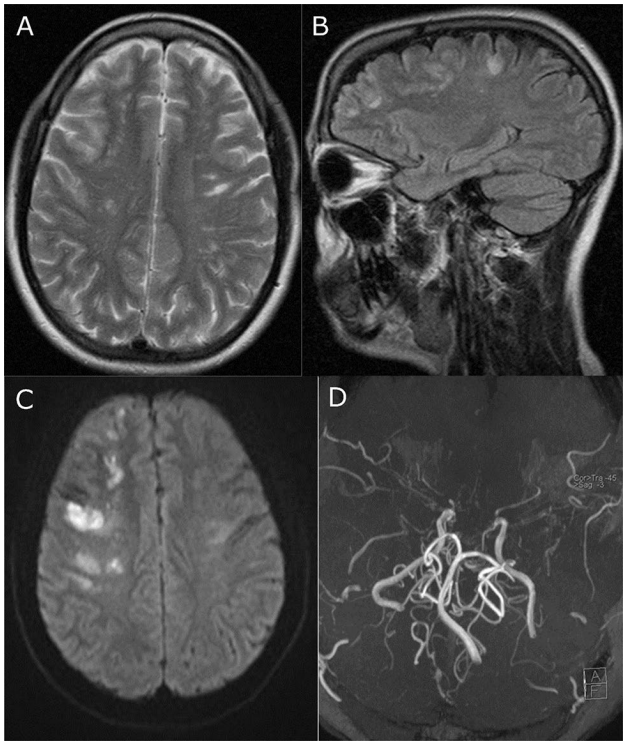

Fig. 4 MRI of a female patient begin of 20 misdiagnosed as MS in 2012 **a, b** despite negative oligoclonal banding in CSF and treated with copaxone for years. **c** Diffusion weighted images and **d** MR angiography when diagnosed as Moyamoya angiopathy in 2017

should include the vascular status and consider MMA in the differential diagnosis. The high rate of misdiagnosis of 34 patients with non-inflammatory MMA as PCNSV suggests that health care professionals are more aware of this very rare vasculitic entity than of non-inflammatory MMA. Awareness for MMA is crucial, and appropriate diagnostic steps [28] including conventional angiography should be taken. With regard to misdiagnoses of stroke-like episodes, the lack of extracranial arteriosclerosis, traditional cardiovascular risk factors, and a younger age should prompt diagnostic re-consideration. In conclusion, diagnosis of frequent neurological diseases like multiple sclerosis should be built not only on positive diagnostic criteria but also on exclusion of differential diagnosis [34], most often by judging if symptoms [33], medical history and examination as well as CSF and MRI are typical [33, 35], and not by broad differential diagnostic laboratory approaches [36].

Our study has strengths and limitations. This is the first study systematically addressing this theme. The strength points of our study are that it builds on a large consecutive cohort of MMA patients at a single center with well-established diagnostic pathway for MMA and other rare cerebrovascular disorders. The main limitation is that data were extracted retrospectively from case files.

Conclusion

In conclusion, our study is the first to systematically address the high frequency of misdiagnosis and delayed diagnosis in a large cohort of European Caucasian patients with MMA.

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Compliance with ethical standards

Conflicts of interest Authors report no conflicting interests.

Ethical approval This study was approved by local ethical committee.

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ORIGINAL ARTICLE

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Factors associated with headache in intravenous immunoglobulin treatment for neurological diseases

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Objectives: To identify possible risk factors influencing the incidence of intravenous immunoglobulin (IVIg) treatment-related cephalalgia in neurological diseases.

Materials & Methods: Retrospective chart review of neurological patients receiving IVIg treatment between July 13, 2017, and August 14, 2017. Patients with MS receiving natalizumab in the same setting were observed as a reference group.

Results: Patients with headache after IVIg infusion (n = 22 infusions) showed a reduced heart rate (by 6.0 ± 8.5 beats per minute [bpm]), but no significant difference in blood pressure. Patients without headache after IVIg infusion (n = 69 infusions) showed a higher systolic blood pressure increase and a stronger reduction in the heart rate (by 5.7 ± 8.6 bpm), compared to patients with headache after IVIg infusion. The infusion rate was significantly slower and age significantly lower in patients developing headache after IVIg infusion. Body temperature was unchanged in both groups. Binary logistic regression analysis revealed that blood pressure at baseline and age significantly influence the occurrence of cephalalgia. In reference, patients receiving natalizumab (ie, shorter infusions/smaller infusion volume), systolic blood pressure, and heart rate decreased, while body temperature increased. Here, one patient developed headache.

Conclusions: Intravenous immunoglobulin-associated headache is not associated with an increased blood pressure after infusion but with a reduced heart rate, a slower infusion rate, female sex and seems to be influenced by baseline systolic blood pressure and age. A reaction to immunoglobulin aggregates, stabilizers, or vasoactive mediators are possible explanations. The absence of an association with body temperature does not suggest a systemic immune response as a cause for headache.

KEYWORDS
adverse effects, headache, intravenous immunoglobulin treatment

1 | INTRODUCTION

In intravenous immunoglobulin (IVIg) treatment, headache and vital sign changes, especially arterial hypo- and hypertension as well as increased body temperature and fever, are common and transient side effects.[1] The general safety profile of IVIg therapy is well established,[2] and headache management has been reviewed.[3] However, the possible underlying mechanisms and patterns of these side effects are not fully clarified yet. In a previous, uncontrolled trial with healthy male volunteers, higher IVIg infusion rates were associated with side effects in general.[4] In this study, we investigated the occurrence of headache related to IVIg therapy and the

possible relationship with sex, age, infusion modalities, and changes of vital sign patterns during IVIg infusion. We hypothesize that cephalalgia after IVIg is related to vital sign changes. The rational of this study was to find possible risk factors influencing the occurrence of IVIg-associated headache in order to increase the quality of life and safety of the patients. Surprisingly, our data suggest that patients presenting with IVIg-related headache were characterized by a decreased blood pressure and a slower infusion rate.

2 | PATIENTS AND METHODS

We conducted a single-center retrospective chart review study at the Department of Neurology, Heinrich Heine University hospital in Düsseldorf, Germany. The study was approved by the ethics committee in Düsseldorf (registry number 6183R). The ethics committee waived the need for consent from the patients due to the retrospective nature of the study. We analyzed infusion protocols of all patients who received IVIg between July 13 and August 14 in 2017. In the aforementioned period, 91 IVIg infusions were administered to 67 patients. 20 of the patients were female (29.9%) and 47 were male (70.1%). Indications for IVIg treatment were chronic inflammatory demyelinating polyneuropathy (CIDP; total 54 patients, 80.6%), multifocal motor neuropathy (MMN; total four patients, 5.97%), myasthenia gravis (MG; total five patients, 7.46%), progressive encephalomyelitis with rigidity and myoclonus (PERM; total one patient, 1.49%), inclusion body myositis (IBM; total one patient, 1.49%), small fiber polyneuropathy (sfPNP; total one patient, 1.49%), and IgLON5-positive encephalitis (IgLON5 + E; total one patient, 1.49%). As a local reference cohort, we analyzed 65 infusion protocols of 65 patients with MS who received natalizumab in the same period of time under the same clinical settings. In contrast to IVIg infusions, natalizumab was applied in a standardized manner to all patients, in a fixed dose (300 mg), a fixed volume (115 mL), and fixed duration of infusion (1 hour). Please note that this natalizumab group may not serve as a direct control for the IVIg group, given the differences with regard to the duration and applied volume of the infusion therapies. Treatment-associated headache has been diagnosed according to the third edition of the International Classification of Headache Disorders (ICHD-3; Secondary Headaches: Headache attributed to the use of or exposure to other substance).[5] Blood pressure, heart rate, and body temperature were measured before and after the infusion and are given as mean ± SD unless otherwise specified. Blood pressure was measured according to the current guidelines.[6] Furthermore, the individual cardiovascular risk profiles, including the risk factors hypertension, diabetes mellitus, sleep apnea, atrial fibrillation, and coronary heart disease, have been analyzed. In the overall analyses, we focused on headache as an independent variable and investigated clinical/vital sign patterns. A detailed overview of the individual patient and treatment characteristics is provided in the Tables S1 and S2. Statistical analyses as indicated were performed using Prism 6.0 (GraphPad); when variables were normally distributed (Kolmogorov-Smirnov test), parametric tests were performed and P values <0.05 were considered significant. For the stepwise forward binary logistic regression analysis, SPSS 20 (IBM) was used.

3 | RESULTS

3.1 | IVIg cohort—analysis per infusion

An overview of the IVIg cohort is provided in Table 1.

The mean age of all 67 patients was 64.6, of all 15 headache patients 59.0 years, and of all 57 patients without headache 65.4 years. As 91 infusions were administered to 67 patients, several patients (n = 19) received more than one infusion. Of note, it occurred that patients did not complain about headache after every infusion. The occurrence of headache was documented after 22 infusions (24.2%) in 15 (7 female, 8 male) individual patients (22.4%). The age of patients complaining about headache after infusion was significantly lower (P = 0.031, Figure S1D). Headache after IVIg infusion was less common in male patients, albeit not statistically significant (chi-square test, one-tailed, P = 0.085, odds ratio 0.45). While the systolic blood pressure of patients without infusion-related headache increased significantly after the infusion, blood pressure remained unchanged in the headache group (Figure 1A). The systolic blood pressure after infusion did not differ between patients with or without headache after infusion (t test, unpaired, P = 0.64).

TABLE 1 Overview of the intravenous immunoglobulin (IVIg) patient cohort

Number of infusions	91 (total)
Number of patients	67
Female	20 (29.9%)
Male	47 (70.1%)
Mean age (y)	66.3
- Patients w/ Headache (total 15)	59
- Patients w/o Headache (total 52)	67.9
Sex proportion	
- Patients w/ Headache (total 15)	7 female/ 8 male
- Patients w/o Headache (total 52)	13 female/39 male
Mean IVIg dosage	0.88 g/kgBW (total)
- Infusions w/ Headache (total 22)	0.82 g/kgBW
- Infusions w/o Headache (total 69)	0.90 g/kgBW
Mean IVIg infusion rate	2.34 mL/kgBW/h (total)
- Infusions w/ Headache (total 22)	2.06 mL/kgBW/h
- Infusions w/o Headache (total 69)	2.43 mL/kgBW/h
Cardiovascular risk factors	
- Patients w/ Headache (total 15)	9 out of 15 (60%)
- Patients w/o Headache (total 52)	33 out of 52 (63.5%)

Cardiovascular risk factors include hypertension, diabetes mellitus, sleep apnea, atrial fibrillation, and coronary heart disease.
g/kgBW, gram per kilogram bodyweight; mL/kgBW/h, mL per kg bodyweight per hour; w/, with; w/o, without.

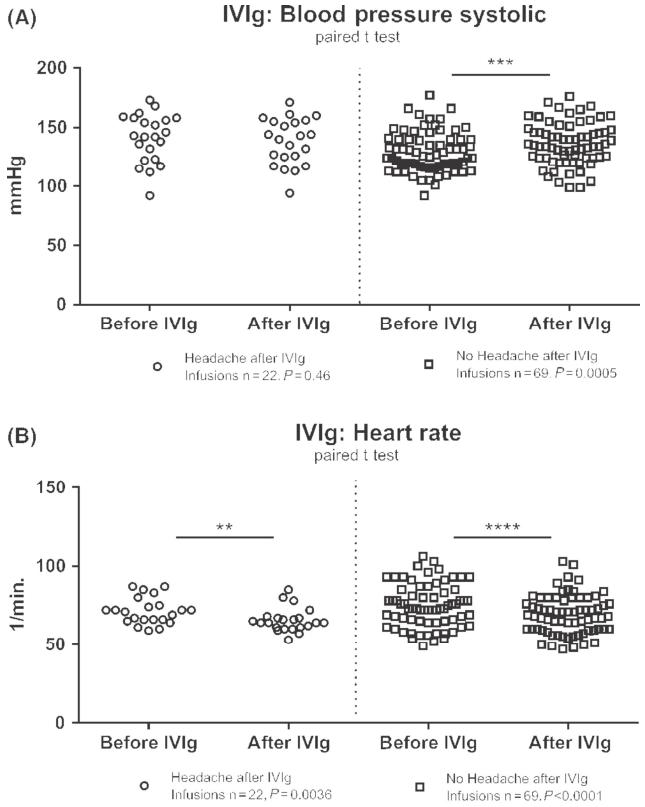

FIGURE 1 Vital signs in patients with and without headache after treatment with intravenous immunoglobulin (IVIg)—analysis per infusion. A, systolic blood pressure before and after infusion; B, heart rate before and after infusion; min., minute. *$P \leq 0.05$, **$P \leq 0.01$, ***$P \leq 0.001$, ****$P \leq 0.0001$

None of the patients who received IVIg had a history of chronic migraine, frequent episodic or chronic tension-type headache, trigeminal autonomic cephalalgias, or other primary headache disorders according to ICHD-3.[5] Moreover, the occurrence of headache was not linked to pre-existing cardiovascular diseases: Nine out of 15 (60%) headache patients had cardiovascular risk factors such as hypertension, diabetes mellitus, sleep apnea, atrial fibrillation, and/or coronary heart disease, while 35 out of 57 (61.4%) patients without infusion-related headache showed a similar constellation. All patients with a history of hypertension were stable regarding their blood pressure on their current medication for at least one year. Overall, the systolic blood pressure before infusion (baseline) was significantly lower in the group without headache after infusion (ie, reduced by 6.29 ± 14.25 mm Hg [mean ± SD]; Figure S2A, *t* test, unpaired, $P = 0.01$). Also, when analyzing the subgroup of patients with hypertension, the systolic blood pressure before infusion was significantly lower in the group without headache after infusion (Figure S2B, *t* test, unpaired, $P = 0.007$). Patients with a history of hypertension showed a trend for higher initial systolic blood pressure (Figure S2C, *t* test, unpaired, $P = 0.051$). Finally, systolic blood pressure was significantly lower at baseline in patients without any of the abovementioned cardiovascular risk factors (Figure S2D, *t* test, unpaired, $P = 0.043$). The infusion duration (Figure S1A) and dosage (Figure S1C) did not differ significantly, but the infusion rate (Figure S1B) was set significantly slower in patients with headache after IVIg infusion.

Several patients received more than one infusion in the aforementioned period. Interestingly, these patients did not complain about headache after every single infusion episode. The occurrence of headache was not associated with a higher IVIg dosage. Of note, patients who received an allergy prophylaxis (prednisolone, ranitidine, clemastine, and/or paracetamol) before IVIg infusion (n = 16 infusions) did not develop headache. None of the patients were pretreated in order to prevent headache. Two patients received nitrendipine 20 mg before IVIg infusion due to systolic blood pressure over 180 mm Hg. Both did not develop headache. Another infusion needed to be discontinued due to severe dizziness (not associated with headache) which resolved spontaneously after 2 hours. In both groups with/without headache, the heart rate was significantly slower after the infusions, with the difference being more pronounced in patients without headache (Figure 1B). We observed no significant difference in body temperature and diastolic blood pressure between both groups (graphs not shown).

All infusions ran more slowly than the maximum recommended infusion rate of 4.8-8.4 mL/kg bodyweight per hour (mL/kgBW/h; Table S1), and the infusion rate was set significantly slower in patients with headache after IVIg Infusion (mean 2.06 ± 0.6 [SD] vs 2.43 ± 0.77 mL/kgBW/h, Table 1). The mean infusion rate of all infusions was 2.34 ± 0.75 mL/kgBW/h. Of those infusions that ran slower than the mean rate (n = 56, infusion rate range 0.72-2.33 mL/kgBW/h), 28.6% (n = 16) infusions were associated with post-infusion headache. For those infusions that ran at the same or a faster rate than the mean (n = 34, infusion range 2.34-4.61 mL/kgBW/h), 17.7% (n = 6) infusions were associated with post-infusion headache (chi-square test, one-tailed, $P = 0.12$, odds ratio 1.87). Of note, the infusion rate was not set at a fixed rate with an infusion pump and therefore retrospectively calculated with the documented bodyweight, infusion volume, and duration. Factors that may influence the individual infusion rate were, for example, iv catheter size and arm position during the infusion. In order to explore factors that may influence the occurrence of post-IVIg cephalalgia, a stepwise forward binary logistic regression analysis including baseline systolic/diastolic blood pressure, baseline heart rate, baseline body temperature, infusion duration, infusion rate, dosage, age, and sex has been performed. Here, higher baseline systolic blood pressure ($P = 0.017$) influences headache the most, followed by age ($P = 0.029$). The other factors showed no significant influence.

3.2 | IVIg cohort—analysis per patient

As already mentioned above, 19 patients received more than one infusion. Of these patients with multiple infusions, five patients are included in both headache and non-headache group in the analysis per infusion as they had both headache and no headache after at least one infusion. Existing data suggest that a hangover effect is present in patients with more than one infusion on consecutive

days.[7] In order to avoid possible bias, we performed an analysis including only one infusion per patient. The results of this analysis do not differ from the analysis per infusion (Figure 2).

3.3 | Local natalizumab reference cohort

An overview of the natalizumab reference cohort is provided in Table 2.

In the observational period, 65 natalizumab infusions were administered to 65 patients under the same clinical settings. 43 of the patients were female (66.2%) and 22 were male (33.8%). The occurrence of mild to moderate headache was documented after 1 infusion (1.5%). No patient had a history of chronic headache disorders or arterial hypertension. After infusion, the systolic blood pressure and the heart rate were significantly decreased while the body temperature was significantly raised (Figure 3A-C). There was no significant difference in diastolic blood pressure (graph not shown).

4 | DISCUSSION

A better understanding of side effects may lead to improved quality of treatment and patient safety as well as therapy adherence.

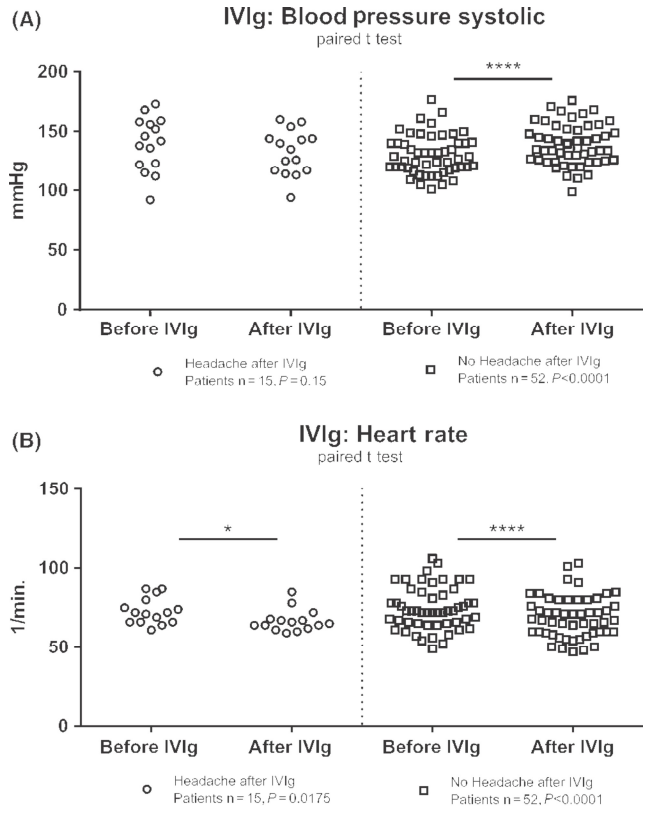

FIGURE 2 Vital signs in patients with and without headache after treatment with intravenous immunoglobulin (IVIg)—analysis per patient. A, systolic blood pressure before and after infusion; B, heart rate before and after infusion; min., minute. *$P \leq 0.05$, **$P \leq 0.01$, ***$P \leq 0.001$, ****$P \leq 0.0001$

TABLE 2 Overview of the natalizumab patient reference cohort. w/ = with, w/o = without

Number of infusions	65
Number of patients	65
Female	43 (66.2%)
Male	22 (33.8%)
Mean age (years)	40.5
- Patients w/ Headache (total 1)	34
- Patients w/o Headache (total 64)	40.6
Dosage (fixed per infusion)	300 mg
Volume (fixed per infusion)	120 mL

The overall incidence of headache in our IVIg cohort is similar to previous reports.[8] IVIg side effects[2] and their management[3] have already been described previously, but have not yet been put into context with clinical factors. Although our study is limited by its retrospective way of conduction and its rather heterogeneous, small cohort with neither a fixed IVIg infusion rate nor dosage, relevant new conclusions can be drawn as we focused on the occurrence of acute headache post-IVIg infusion. Analyzing the relation of headache with vital sign patterns, a paradox picture evolves: Patients without headache after administration of IVIg showed an increased blood pressure after IVIg infusion, whereas the blood pressure of patients with headache after infusion was unchanged. However, baseline blood pressure was significantly higher in the headache group than in the no headache group. Interestingly, the infusion rate was significantly slower in patients with headache after IVIg infusion. This constellation may suggest that starting an IVIg infusion at a fixed slower rate may not prevent headache, but, as described previously,[3,9] that reducing the infusion rate after the occurrence of headache may improve headache symptoms. Alternatively, as described and discussed in a previous retrospective study, the unexpected lower infusion rate in patients developing headache after infusion might be due to the retrospective manner of the infusion rate calculation.[2] Of note, our retrospective study design cannot be used to draw conclusions regarding the cause effect relationship of the IVIg infusion rate. Also, the overrepresentation of patients without headache may be factor influencing the vital sign differences. In order to rule out and explore a possible effect, a prospective, randomized, controlled, double-blind study with fixed infusion rates as independent variables and a fixed IVIg dosage would be necessary. Of note, the daily dosage did not differ between patients with and without headache after IVIg (Figure S1C). Surprisingly, patients without headache after IVIg tend to have a lower systolic blood pressure before infusion, when compared to the group with headache. In both groups, the heart rate decreased, but stronger in patients without headache. We cannot rule out that these vital sign patterns are solely due to the different infusion rate. Male patients as well as older patients seem to be at a lower risk of developing headache. IVIg dosage and infusion duration were not clearly associated with post-infusion headache. Of note, regarding the regression analysis,

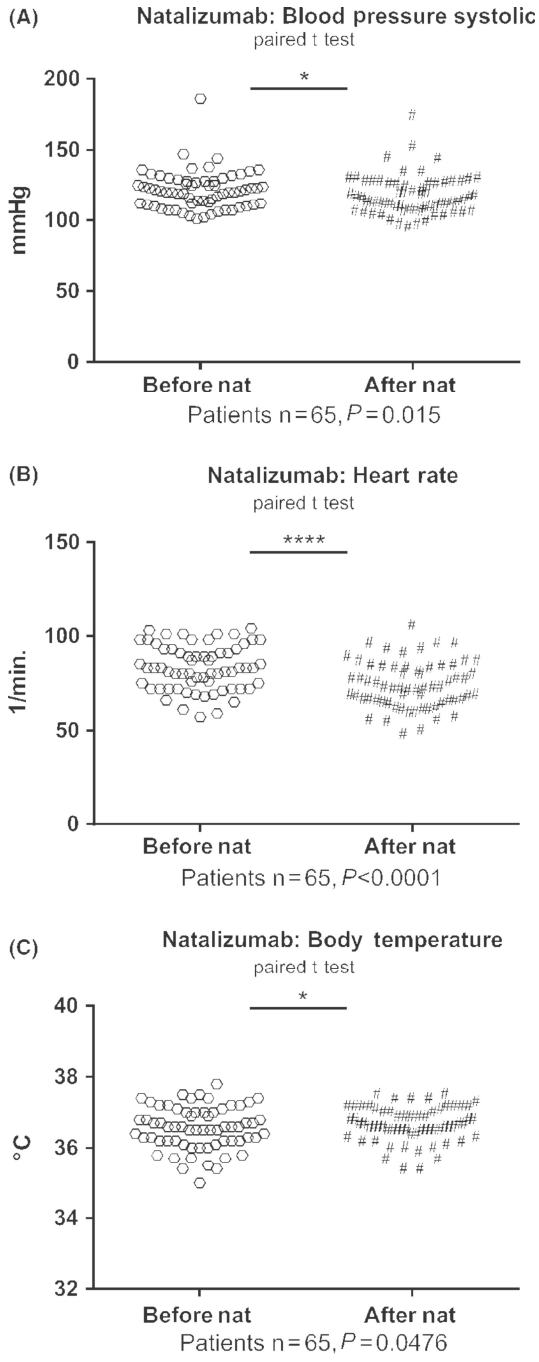

FIGURE 3 Vital signs in multiple sclerosis patients treated with natalizumab (Nat) under the same clinical settings as the IVIg-treated patients. A, systolic blood pressure before and after infusion; B, heart rate before and after infusion; C, body temperature before and after infusion; min., minute. *$P \leq 0.05$, **$P \leq 0.01$, ***$P \leq 0.001$, ****$P \leq 0.0001$

baseline systolic blood pressure and age both influence post-IVIg cephalalgia. Therefore, our hypothesis cannot be refuted. Of note, in the local reference cohort, consisting of younger and predominantly female patients receiving natalizumab infusions with a shorter treatment duration and smaller infusion volume, heart rate diminishes as well, but the systolic blood pressure is lower, the body temperature is higher and headache after infusion was virtually absent.

Headache after administration of IVIg seems to be an infusion rate-related specific side effect, since one would expect that patients with a higher blood pressure and body temperature due to a systematic (immune) response tend to develop headache. Additionally, hormonal factors may also play a role in developing headache after IVIg infusion, as headache seems to occur less frequently in male patients.

Existing data suggest that hydration is a key factor in developing headache after IVIg infusion.[10,11] Since patients with headache after infusion tend to have a higher systolic blood pressure than patients without headache before infusion, dehydration as a major factor is rather unlikely. Our findings are in line with the current recommendations: Evidence for rehydrating before administration of IVIg is rather low (evidence level IV, recommendation D) compared with switching to application of subcutaneous immunoglobulin (SCIg; evidence level I, recommendation A), premedication with paracetamol or nonsteroidal anti-inflammatory drugs (NSAIDs; evidence level II, recommendation B) or lowering the infusion rate (evidence level III, recommendation C).[12] The positive effect of SCIg on the severity of headache compared with IVIg has already been analyzed.[7] Of note, patients who received an allergy prophylaxis before IVIg in our cohort did not develop cephalalgia.

Regarding the mechanisms responsible for infusion-related headache, potential explanations encompass aggregated immunoglobulin molecules (which may cause complement activation), antigen-antibody reactions, possible vasoactive mediators, or stabilizers that may have been used during the manufacturing process.[13] Since no significant increase in body temperature and blood pressure occurred in the IVIg group with headache, we found no direct evidence for an immune response such as complement activation or antigen-antibody reactions to be a cause of headache. On the other hand, since we observed that patients with allergy prevention did not develop headache an immune system involvement can also not be ruled out. An increased plasma viscosity as a trigger for hypertension is also unlikely.[14]

In summary, our data suggest that post-infusion headache as a specific side effect of IVIg is associated with a slower infusion rate, a decrease in blood pressure and female sex and seems to be influenced by baseline systolic blood pressure and patient age. Dehydration and/or a systemic immune response as a cause are rather unlikely. We conclude that risk factors related to IVIg-associated headache exist and are clinically relevant. Important findings of our study are negative findings like the lack of association between headache and increased blood pressure or body temperature. Further studies are warranted to confirm these links in order to better prevent IVIg-mediated headache.

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CONFLICT OF INTEREST

Jonas Graf received travel/meeting/accommodation reimbursements from Biogen, Merck Serono, and Sanofi Genzyme. Jens

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AUTHOR CONTRIBUTIONS

Jonas Graf, MD, involved in study concept/design, acquisition/analysis/interpretation of data, and drafting of the manuscript; Jens Ingwersen, MD, involved in acquisition/analysis/interpretation of data and revision of the manuscript; Klaudia Lepka, PhD, Philipp Albrecht, MD, Hans-Peter Hartung, MD PhD FRCP, and Marius Ringelstein, MD, involved in analysis/interpretation of data and revision of the manuscript; Orhan Aktas, MD, involved in study concept/design, acquisition/analysis/interpretation of data, and drafting and revision of the manuscript.

DATA AVAILABILITY STATEMENT

All available data have been included in this manuscript and the Supporting information.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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ORIGINAL COMMUNICATION

Efficacy of STA–MCA bypass surgery in moyamoya angiopathy: long-term follow-up of the Caucasian Krupp Hospital cohort with 81 procedures

Markus Kraemer[1,3] · Rusen Karakaya[1] · Toshinori Matsushige[2] · Jonas Graf[3] · Philipp Albrecht[3] · Hans-Peter Hartung[3] · Peter Berlit[1] · Rudolf Laumer[4] · Frank Diesner[4]

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Abstract

Background Despite the consensus on the efficacy of revascularizing surgery in moyamoya angiopathy (MA) in Asia, the indication in Caucasian moyamoya patients is controversially discussed.

Objective The efficacy of revascularizing surgery in adult European patients with MA should be clarified.

Methods This study retrospectively analyzed the rate of further strokes and hemorrhages as well as MRI and Duplex ultrasound features during long-term follow up after STA–MCA bypass.

Results Eighty-one STA–MCA bypass procedures in 54 patients with MA operated in one single German institution were analyzed. All 54 patients (100%) were Caucasians. After two diffusion restricted spots in MRI perioperatively (2.5%) and short-lasting symptoms directly after surgery, no patient experienced further new symptoms related to stroke or hemorrhages nor no new gliotic scars or microbleeds on MRI for 38.2 months. Duplex ultrasound 3 months after surgery documented bypass patency in 100% and sonographic sign for good relevance of the bypass in 96.2%. In addition, the diameter of the donor vessel had increased in 89.9% as an indicator for the relevance of the bypass. Semi-quantitative analysis of perfusion changes in the operated hemispheres demonstrated an increase in perfusion in the MCA territory in 56 of 74 (75.7%) hemispheres 36.7 months after surgery. In MRA images, a reduction of typical moyamoya collaterals was found in 65 of 79 hemispheres (82.3%) after a mean of 37.2 months.

Conclusion Direct STA–MCA bypass is an effective therapy in Caucasian patients with hemodynamically compromised MA.

Keywords Moyamoya angiopathy · Bypass surgery · Europeans · Efficacy · Stroke

Introduction

Moyamoya angiopathy (MA) is a rare and chronic occlusive bilateral cerebrovascular disease of the terminal internal carotid artery (ICA) and its proximal branches, especially the anterior cerebral artery (ACA) and the middle cerebral artery (MCA). As a result of these stenoses, brain tissue in the ACA and MCA territories is deprived of adequate perfusion, triggering the formation of the large networks of collateral vessels that led to the naming of the disease (moyamoya means cloud or fog in Japanese). The most common clinical manifestation of MA is cerebral ischemia, typically affecting the territories of the MCA and ACA as well as intracerebral and subarachnoidal hemorrhages. Other symptoms, such as limb-shaking transient ischemic attack (TIA), syncope, intellectual decline, epilepsy, and psychopathological changes, may be observed. Movement disorders and headache are also

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not rare [1–3]. Non-surgical management aims at preventing complications of the disease using medical therapies. These include antiplatelet therapy to minimize the risk of embolic ischemic events [4, 5]. Furthermore, it is advisable to ensure good blood pressure control, even though only few studies have addressed this point [6]. Surgical management strategies play a key role in MA patients with hemodynamic perfusion deficits [7]. Since MA cannot be cured, bypass surgery is performed to reduce ischemia and hemorrhagic events. The aim of direct and indirect revascularization procedures is to restore adequate cerebral perfusion by creating anastomoses between extracranial and intracranial blood vessels. The principle of direct bypass surgery is to create an anastomosis between the superficial temporal artery and an intracranial artery, in most cases the middle cerebral artery. Ideally, this results in the rapid restoration of cerebral blood flow. Direct bypass surgery aims at diminishing the incidence of hemodynamic stroke and it is hoped that the risk of cerebral hemorrhage can also be reduced by relieving the load on the fragile collateral vessels [8–10]. In Asian patients, the benefits and potential complications of MA bypass surgery have been studied extensively [9, 11–17].

However, it is known since 1985 that extracranial–intracranial revascularizing surgery is ineffective in non-MA patients with arteriosclerotic diseases [18–20]. In line with this, European neurologists are still often reluctant to indicate bypass surgery also in adult MA, presumably due to assumption of missing benefit in Caucasian adult patients.

Objective

Outside of Asia, the literature about the efficacy of revascularisation surgery especially in European Caucasians is sparse and clinically relevant questions are still unsolved.

Therefore, it is important to analyze the efficacy based on neurological examination, MRI and Duplex sonography in adult European patients with MA.

Patients and methods

To evaluate the benefits of bypass surgery in European Caucasian patients with MA, data from patients who met all diagnostic criteria of the Research Committee of the Japanese Ministry of Health and Welfare [7] for MA and underwent bypass surgery at the Alfried Krupp Hospital, Essen, between 2008 and 2016 were analyzed. All patients were of Caucasian ethnicity living in Germany. Those patients with Asian and non-Caucasian family background were excluded from participation in this study. All patients were interpreted as having idiopathic moyamoya disease and all were adults due to referring bias to our adult moyamoya center. To better quantify the success of bypass surgery, the data of these patients were divided up by hemispheres. The study was retrospective and the decisions for all procedures and therapy were based on clinical reasoning and are not influenced by the study. Indication of surgery based on medical history, clinical examination and MRI and perfusion studies as well as MR and conventional angiography. The study was approved by the local ethics committee and informed written consent was obtained from all patients.

Retrospective analysis

Clinical follow-up after 3 months

Based on outpatient clinic reports and hospital discharge letters, postoperative complications were evaluated in all patients separated in different hemispheres both at the time of discharge from acute care, i.e., directly after surgery, and at month 3 of the follow-up.

Long-time clinical follow-up

The state of health including the neurological examination was assessed at the last clinical follow-up based on outpatient clinic reports. These ratings were based on the detailed neurological history and physical full body, neurological and psychiatric examination done by a single specialized neurologist (MK). Complaints not directly related to ischemic or hemorrhagic manifestations of MA-like headaches, visual aura in migraine or carpal tunnel syndrome were not included.

Assessment of bypass patency comparing preoperative Duplex sonography with Duplex sonography 4 days and 3 months, postoperatively

Color duplex sonography was used to postoperatively analyze whether the pulsatility of the superficial temporal artery, by nature an extracranial artery, transformed to an intracranial signal pattern [21]. Color duplex sonography was performed at day 4 after surgery and at 3 months after surgery. In addition, by applying pressure to the STA while simultaneously scanning the MCA by Doppler sonography, it was determined whether a compression effect was present (Fig. 1). This in turn was interpreted as an indicator for the hemodynamic contribution of the bypass. This maneuver was performed 3 months after surgery.

Measurement of new gliosis comparing preoperative MRI with MRI after 3, 6, and 12 months and at long-term follow-up postoperatively

For each operated hemisphere, the pre- and postoperative MRI findings obtained at day 6 postoperatively as well as

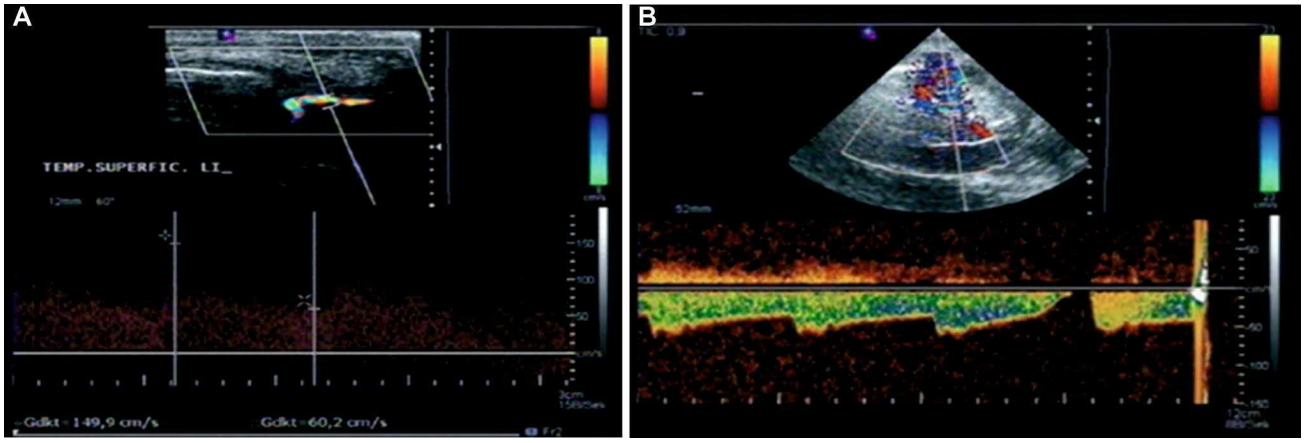

Fig. 1 **a** Intracranial signal pattern of extracranial superficial temporal artery as sign of bypass patency. **b** The compression maneuver of the superficial temporal artery with erasure of flow in middle cerebral artery as sign of bypass relevance

at months 3, 6 and 12 postoperatively and at the last follow-up visit were analyzed for signs of new or interim manifest cerebral ischemia or hemorrhage. For each patient, MRI included at least axial T1-weighted images, axial gradient echo T2*-weighted images, axial Fluid Attenuated Inversion Recovery (FLAIR) images, and axial T2-weighted fast spin-echo images as well as diffusion-weighted images.

Assessment of the hemodynamic situation comparing preoperative MR perfusion imaging with MR perfusion at long-term follow-up

In contrast-enhanced brain MRIs, perfusion-weighted images, e.g., the mean transit time (MTT), were specifically assessed. MTT corresponds to the average time, in seconds, that an erythrocyte spends within a determinate volume of the capillary circulation. Thus, an increase in cerebral blood flow in the presence of an unchanged blood volume indicates a shorter MTT and consequently improved perfusion. Here, the vascular territories of MCA, basal ganglia and cerebellum—preoperatively and of the MRI of the last visit in long-term follow-up—were of special interest. In all patients, the individual patient's MTT value in the cerebellar region was used as the perfusion reference value, as this region is not affected by MA (Fig. 2). In addition, uniformity of measurements was ensured for all regions of interest. For the cerebellum, it was 100 mm^2, for the basal ganglia 311 mm^2 and for the MCA territory 1208 mm^2. Perfusion changes in the MCA territory of the left hemisphere were calculated as follows:

MCA preoperative/cerebellum preoperative $= X$,

MCA postoperative/cerebellum postoperative $= Y$.

Subsequently, the preoperative-to-postoperative change rate was calculated using the following formula:

$$(Y - X) / X \times 100.$$

This formula was adapted on the study of Saito and colleagues [22] to enable comparison of MR perfusion preoperatively and at last follow-up visit postoperatively.

The result is a number without a unit, as the formula contains ratios and their percentage values. Negative numbers indicate an increase in perfusion during the postoperative follow-up, while positive numbers indicate a postoperative decrease in perfusion compared with the preoperative situation. The preoperative MR perfusion imaging per hemisphere was compared with those images at the last clinical follow-up.

Measurement of collaterals comparing preoperative MR angiography (MRA) with MRA at long-term follow-up

MR angiography was used to visualize the collateral vessels typically seen in MA within the basal ganglia. Using a two-rater technique, these were counted within a defined area of the affected hemisphere. Subsequently, the means were calculated. Preoperative MRA images of each hemisphere were compared with the postoperative images obtained at the last follow-up (Fig. 3). Reduction of collaterals could be interpreted as a sign for relevant hemodynamic contribution of the bypass and reduction of bleeding risk.

Analysis of superficial temporal artery comparing preoperative MRA with MRA at long-term follow-up

An increase in the size of the superficial temporal artery (STA), as demonstrated in preoperative versus postoperative comparison at last follow-up using MRA was

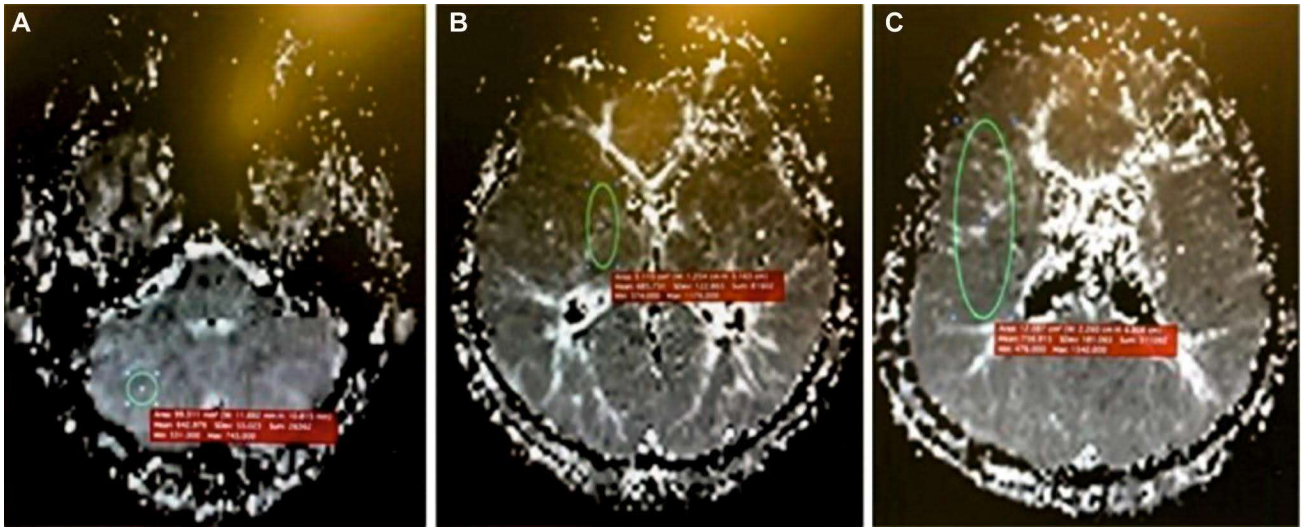

Fig. 2 The method of standardized assessing of the improvement of the MR perfusion images in the cerebellum as normal area, in the basal ganglia and in the MCA territory

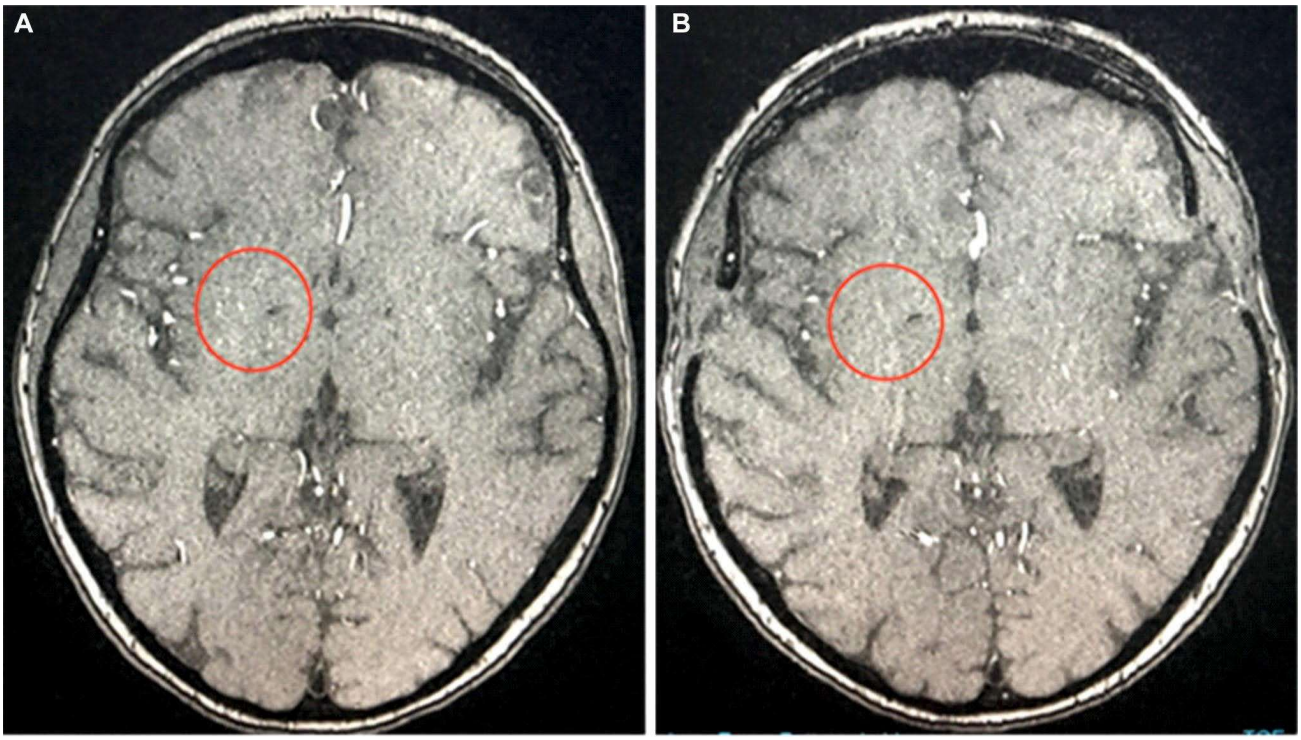

Fig. 3 White spots in MRA indicating moyamoya collaterals before (left) and after (right) surgery

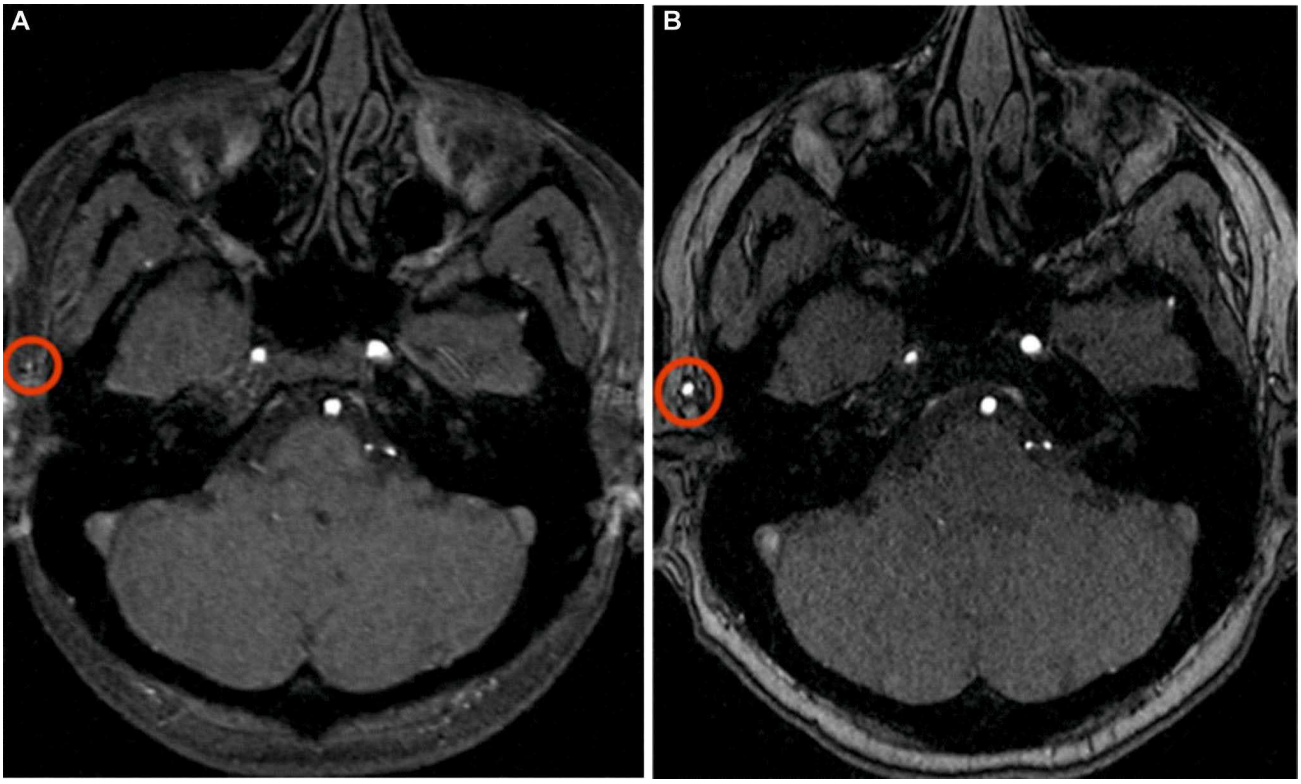

Fig. 4 Comparison in the diameter of the STA in the MRA before (left) and after (right) surgery

interpreted as another sign of successful STA–MCA bypass surgery (Fig. 4).

Prospective survey

Furthermore, a subjective self-rating questionnaire on patient satisfaction was handed out or mailed to patients. In addition, the option of conducting telephone interviews with patients was available. The aim of the prospective questionnaire was to systematically collect data on the satisfaction preferably in an anonymous manner without bias due to direct interview by treating physician.

Results

Demographic data

Eighty-one surgical procedures were performed using the STA as donor vessel and a distal branch of the MCA as acceptor vessel in 54 patients. The participants were 15 males and 39 females. The mean age at the time of first surgery was 39.1 years (mean, median 39.5 years, standard deviation 12.8). The great majority of patients had bilateral MA (40 of 54, 74.1%), only 14 patients were suffering from a unilateral variant.

Clinical follow-up after 3 months

After ten procedures (12.3%), patients complained new symptoms within 3 months after surgery. All these symptoms were transient for seconds or minutes and completely suspended after 3 months. In particular, after six procedures (7.4%), patients suffered from short-lasting prickling episodes diagnosed as focal sensory seizures. After two procedures (2.5%), a focal motor seizure and after one procedure (1.2%) a generalized seizure occurred in one patient within 3 months after surgery. One patient (1.2%) complained of short-lasting amnestic aphasia.

Long-time clinical follow-up

All 54 patients with 81 hemispheres who were followed up in our MA outpatient clinic were completely free of new or interim symptoms qualified as hints for new TIA or stroke in a long-term of follow-up of 38.2 months postoperatively (median 32.22, standard deviation 26.51).

Measurement of bypass patency comparing preoperative Duplex sonography with Duplex sonography 4 days and 3 months postoperatively

All 81 hemispheres were examined by Duplex sonography at day 4, as well as 3 months after surgery. All examinations revealed a sufficient bypass with an intracranial signal pattern of STA (100%) at day 4 as well 3 months after surgery. In 79 evaluable hemispheres a compression maneuver was done 3 months after surgery. In 38 of 79 hemispheres (48.1%), Doppler sonography revealed no flow of the MCA during the short compression maneuver of the extracranial STA. In 38 hemispheres (48.1%), a reduction of the flow of the MCA (but not a zero flow like in those other 38 ones) was found in Doppler sonography during this compression maneuver. In three hemispheres (3.8%), this compression effect was not found.

Measurement of new gliosis comparing preoperative MRI with MRI after 6 days, 3, 6, and 12 months and at long-term follow-up

In 2 of all 81 (2.5%) hemispheres, postoperative diffusion abnormalities were identified in MRI at postoperative day 6. Both the lesions were, according to their morphology, emboligenic and occurred during the cessation of antiplatelet therapy. One of these two strokes was clinically relevant; the other one was asymptomatic. No gliosis or microbleeds were detected at month 3, nor 6 or 12 months postoperatively or in long-term follow-up after surgery. The rate of strokes in hemispheres during further follow-up was 0 (except for above-mentioned perioperative risk of two diffusion abnormalities in the first week). The mean duration of long-term follow-up for 81 hemispheres was 38.2 (median 32.2, standard deviation 26.5).

Measurement of hemodynamic situation comparing preoperative MR perfusion imaging with MR perfusion at long-term follow-up postoperatively

In 49 patients with 74 hemispheres, sufficient preoperative MR perfusion imaging and at last follow-up 36.7 months (median 32.2 ± 26.3) after surgery were available.

Among these 74 hemispheres, the average change rate was −13.4 (median −14.0, standard deviation 25.9) in the MCA territory and −5.4 (median −4.7, standard deviation 21.3) in the basal ganglia. This corresponds to an average increase in perfusion of 13.4% in the MCA territory and 5.4% in the basal ganglia after a mean of 36.7 months. In 56 of 74 (75.7%) hemispheres, an improvement was depicted in the MCA territory and in 41 of 74 (55.4%) in the basal ganglia territory.

Measurement of collaterals comparing preoperative MRA with MRA at long-term follow-up

In 79 hemispheres of 53 patients, comparison of preoperative MRA with MRA at last follow-up after a mean of 37.23 months (median 32.22, standard deviation 26.07) was feasible.

In 65 of 79 hemispheres (82.3%), a decrease in moyamoya collateral vessels in basal ganglia was observed. In six hemispheres (7.59%), more collaterals were found after 37.23 months postoperatively. In eight (10.1%) hemispheres, the number of spots was the same. Altogether, the decrease was −33.04% (median −40.0%, standard deviation 41.16).

Analysis of STA comparing preoperative MRA with MRA at long-term follow-up

In 79 hemispheres of 53 patients, comparison of preoperative MRA with MRA at the last follow-up after a mean of 37.23 months (median 32.22, standard deviation 26.07) was feasible. In these 79 hemispheres, the diameter of STA increased by 49.23% (median 42.86%, standard deviation 36.94) at last follow-up postoperatively compared to the preoperative measurement. In 71 of the 79 analyzed hemispheres (89.9%), an increase in STA diameter was noted. The average increase rate in STA diameter was 49.23%. More specifically, in 36 STAs, the increase was more than factor 1.5 and in 35 lower than 1.5 times.

Prospective survey

Fifty-four patients completed the questionnaire (15 male and 39 female patients); the mean age of all MA patients who participated in the survey was 39.1 years at the time of first surgery. The mean self-reported patient satisfaction was of 9.2 (median 10, standard deviation 1.26) on the NRS from 0 to 10.

Discussion

In Asia, bypass surgery is recognized as a method for the prevention of hemodynamic and hemorrhagic stroke in patients with MA.

For pediatric Asian patients, it was shown that non-surgical management was associated with a poor prognosis [23, 24]. In adult patients with MA, the risk of ischemic or hemorrhagic stroke is very high in Asians as well as in non-Asian patients.

Outside Asia, Guzman et al. found that from 171 patients with a history of TIA, 91.8% were free of transient ischemic attacks after 1 year or later. However, only 59% of this ethnically mixed cohort were of Caucasian origin. The study of Hallemeier et al. found a 5-year stroke risk for the affected hemisphere in case of bilateral disease of 82% [25]. Likewise, Kraemer et al. revealed a 5-year stroke risk of approximately 80% [26].

However, in European Caucasian patients study data for the indication of bypass surgery are sparse [27–30]. As a first attempt, the French guidelines published just recently aimed to clarify clinical practice of MMA in Europe based on the literature analysis [31].

In 2016, Ha et al. conducted a retrospective study evaluating the efficacy of MCA–STA bypass surgery in adult Asian patients with MA of the ischemic type. The study included 31 patients who underwent 41 direct bypass surgeries between 2006 and 2014. In addition, postoperative and perioperative complications as well as angiographic and clinical outcomes were analyzed [32]. No further ischemic event was observed in 93.5% of patients over a follow-up period of 35 months; the remaining two patients had TIAs. Ha et al. concluded that bypass surgery is a safe and efficient method to reduce the risk of future ischemic events. This was in line with a metaanalysis including 732 hemispheres [16], which demonstrated that bypass surgery is effective in symptomatic MA [16].

Despite these encouraging data from Asia [33] and the US, bypass surgery is often not indicated in adult European Caucasians due to lacking evidence of efficacy.

The majority of neurologists are still skeptical due to the inefficacy of bypass surgery in patients with atherosclerotic disease [18–20]. In 1985, an international randomized study by the EC-IC Bypass Study Group found no advantage for bypass surgery in patients with non-MA symptomatic atherosclerotic disease compared to a control group despite a postoperative bypass patency rate of 96% [18].

The results of the prospective Carotid Occlusion Surgery Study (COS) randomized trial published in 2012 were similar [34]. Despite an excellent bypass patency of 98% and an improved hemodynamic situation, STA–MCA bypass surgery failed to provide an advantage over best medical care in these patients with atherosclerotic stenoses. In the intention-to-treat (ITT) analysis, the risk for subsequent stroke in patients who underwent bypass surgery was 22.7% and in patients who received best medical care 21% [35].

Therefore, the key question addressed in our study was the efficacy of bypass surgery in Caucasian patients in reducing the risk of future ischemic and hemorrhagic events. Moreover, the patency and the functional relevance of bypasses should be clarified. Our detailed study was based on an accurate clinical follow-up in one German specialized center with preoperative examinations, Duplex sonography and MRI as well as postoperative controls directly after surgery, after 3, 6, and 12 months and in the long-term follow-up.

With regards to the safety of bypass surgery, we found that only 2 of 81 (2.5%) operated hemispheres showed signs of postoperative ischemia in MRI after 6 days which appeared to be caused by embolic events and occurred during a period of interruption of aspirin therapy. Only one of the two embolic ischemic lesions was clinically manifest. At months 3, 6 and 12 postoperatively and in long-term follow-up of 38.2 months, no additional manifest ischemia or bleeding was diagnosed based on accurate clinical history taking, neurological examination and Flair, T2 and T2* MR imaging.

Concerning efficacy of the bypass, duplex sonography after 3 months documented an impressive 100% bypass patency. The short compression maneuver of the superficial temporal artery resulted in a reduction or erasure of the Doppler flow in the MCA in 96.2% of hemispheres. This maneuver was invented by our research group and was reported to be indicative of a good hemodynamic contribution of the bypass [36]. Moreover, this study underlines that Duplex sonography represents an elegant and noninvasive method for the clinical follow-up of bypass patency and functional relevance [36–38]. In our experience, diagnostic angiography is not needed to be repeated after the first diagnosis in view of the small but evident serious risks and as it does not reveal additional clinically relevant of information compared with Duplex sonography [39, 40].

Moreover, the increase in diameter of the donor vessel depicted in MRA in 89.9% of hemispheres also argues for the functional relevance of the bypass.

The semi-quantitative analysis of perfusion changes in the operated hemispheres demonstrated an increase in perfusion in the MCA territory in 56 of 74 (75.7%) hemispheres and in the basal ganglia in 41 of 74 (55.4%) hemispheres. Even though the percent increase in perfusion may appear low with 13.4% and 5.4%, respectively, the observed significant reduction in moyamoya collaterals suggests that bypass surgery is also hemodynamically effective. However, as a limitation, it should be noted that the mean transit time per se is not a suitable parameter for the quantitative comparison and that the formula used—which is adopted from a SPECT study—may underestimate the actual improvements in perfusion [22]. This semi-quantitative measure can only indirectly determine the benefit of bypass surgery. Adopting this formula was one attempt to quantify the visual impression of improvement on MRI in daily experience (Fig. 5).

Though this method demonstrated only minor improvement, there were good clinical outcomes with no further gliosis or microbleeds in MRI within 38.2 months after surgery.

The reduction in typical moyamoya collaterals in 65 of 79 hemispheres (82.3%) may be a correlate for the reduction of a future risk of hemorrhage [37, 41, 42].

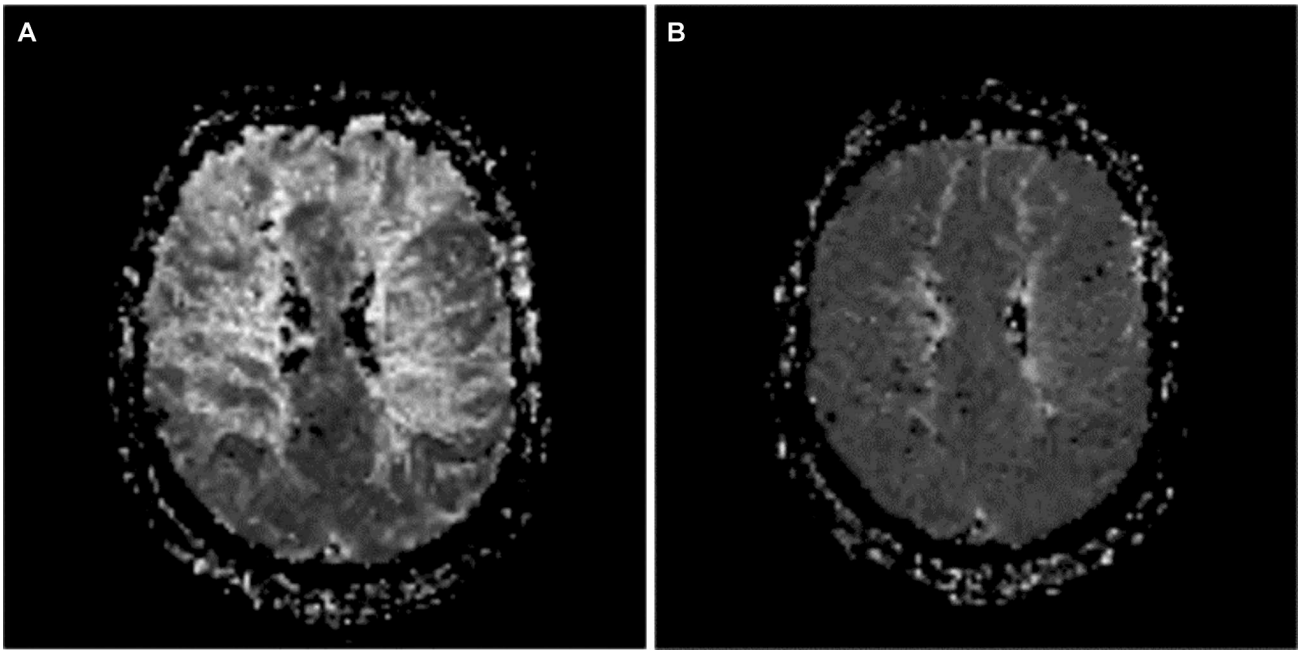

Fig. 5 **a** Preoperative MR perfusion (white areas are hemodynamic insufficient and grey areas are of good perfusion). **b** Postoperative MR perfusion of the same patient (white areas are hemodynamic insufficient and grey areas are of good perfusion)

In conclusion, this study demonstrates efficacy of STA–MCA bypass surgery in mainly European Caucasian patients with MA. The strength of this study is the large and meticulously characterized cohort with 81 operated hemispheres and the detailed follow-up. However, we have to acknowledge that these extremely good postoperative results were based on a single neurological and neurosurgical expert center from one neurosurgeon (FD) and one neurologist (MK) and are, therefore, not necessarily transferable to other centers. Moreover, a crucial point for achieving such excellent surgical and clinical results is the correct indication for the bypass based on medical history, MRI, perfusion studies as well as MR- and conventional angiography.

Summary/conclusion

The encouragingly positive outcome within 38.2 months underlines that bypass surgery should be a therapeutic option in hemodynamic compromised Caucasian patients with MA. Therefore, indication for revascularization surgery should be based on the medical history and hemodynamic studies to estimate the future risk for stroke and hemorrhage. This study shows excellent efficacy within 38.2 months after surgery.

An interdisciplinary neurological and neurosurgical approach is advisable and referral to specialized moyamoya centers is recommended, as it is a rare disease in Europe.

Compliance with ethical standards

Conflicts of interest There is no conflict of interest.

Ethical standards The study was approved by the local ethics committee and informed written consent was obtained from all patients.

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ORIGINAL COMMUNICATION

Moyamoya angiopathy: early postoperative course within 3 months after STA–MCA–bypass surgery in Europe—a retrospective analysis of 64 procedures

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Abstract

Background Despite the consensus on the necessity of revascularizing surgery in Moyamoya angiopathy in Asia, the indication in Caucasian Moyamoya patients is discussed controversially.

Objective The safety of revascularizing surgery in Europe should be clarified.

Methods This study retrospectively analyzed the rate of complications as well as clinical symptoms within the first 3 months after bypass surgery between superficial temporal artery and middle cerebral artery (STA–MCA).

Results 64 direct bypass procedures in 45 patients (95.5% Caucasians) were analyzed. The magnetic resonance imaging at day 6 showed subdural hematoma in 60.3%. The mean diameter of these hematomas on magnetic resonance imaging was 5.1 mm (SD 3.4 mm) and increased in 25% at follow-up. No difference was found between those patients with early (day 1) or late (day 7) restarts of antiplatelet therapy. Magnetic resonance imaging at day 6 revealed hyperperfusion syndrome after six of 64 procedures (9.3%). Three of these six had clinical symptoms; two-thirds were transient within seconds. Magnetic resonance imaging depicted stroke after seven procedures (10.9%). Five of these seven patients had no new symptoms. Altogether, after ten procedures (15%), patients complained about clinical symptoms. These were all transient. No new transient ischemic attacks occurred during the 3 month follow-up and no new lesions were detected in magnetic resonance imaging. Only two patients underwent surgery for asymptomatic subdural hematoma. All other subdural hematomas resolved spontaneously.

Conclusion Revasculating surgery is a safe procedure in Caucasian patients with Moyamoya angiopathy. The observed complications have a good prognosis.

Keywords Risks · Early postoperative course · Moyamoya angiopathy · Subdural hematoma · Caucasians

Background

Moyamoya angiopathy (MMA) is a non-arteriosclerotic vasculopathy characterized by progressive stenoses and occlusions of the intracranial internal carotid arteries (ICA) and proximal parts of middle (MCA) and anterior cerebral arteries (ACA) on both sides. Due to hemodynamic insufficiency, children and young adults with MMA have a high risk for transient ischemic attacks (TIA) and stroke. In addition to hemodynamic stroke, thrombotic material may also arise locally at the stenoses due to hemodynamic insufficiency and a reduced washout. Moreover, the extensive "Moyamoya" collaterals are fragile and bear a high risk for cerebral hemorrhage. The direct bypass surgery (EC/IC bypass) is mainly characterized by creating an anastomosis between the extracranial superficial temporal artery (STA) and a distal branch

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of the MCA (STA–MCA–bypass). The goal is to achieve a rapid restoration of cerebral perfusion in adult and pediatric patients with MMA and to reduce the risk of future ischemic stroke [1]. It is also intended to decrease the risk of cerebral hemorrhage by diminution of the fragile collateral networks. Indirect bypass techniques include the implantation of highly vascularized tissue like muscle or omentum to the brain surface. Indirect bypass surgery is mainly performed in young children when the donor artery STA is too small for direct bypass techniques.

While it is known since 1985 that extracranial–intracranial revascularizing surgery is ineffective in arteriosclerotic diseases [2–4], there is a common consensus among Asian experts that bypass surgery is beneficial in hemodynamic compromised stages of MMA [5–9].

As a first attempt, the French guidelines published just recently, aimed to clarify clinical practice of MMA in Europe based on literature analysis [10]. However, outside of Asia, study data for the indication of bypass surgery are sparse [11, 12]. Therefore, it is important to analyze the risks of direct bypass surgery. Asian studies [13] have reported hyperperfusion syndrome [14, 15], postoperative ischemia [16], and seizures [17] as the main complications after bypass surgery. Postoperative subdural hemorrhages following bypass surgery are nearly completely neglected in the scientific literature [13, 18].

In this study, we aimed to characterize the development of subdural hematomas in the postoperative time course and investigate the rates of spontaneous restitution and the percentage of patients requiring neurosurgical interventions. In addition, we attempted to elucidate if the timepoint of restarting antiplatelet therapy after bypass surgery has an influence on the risk, extent, and prognosis of postoperative subdural hematoma.

Objective

This study aimed to analyze safety of STA–MCA–bypass in Europe in consecutive patients of dominantly Caucasian family origin.

Specifically, we sought to analyze the early postoperative course after STA–MCA–bypass surgery to address the following questions: is there a difference in bleeding complications with early re-initiation of aspirin or clopidogrel? On the other hand, is the incidence of stroke increased in patients with longer intermission of antiplatelet therapy? Which patients have clinical symptoms early after surgery? How is the prognosis of complications within 3 months after surgery?

Methods

We retrospectively analyzed the rate, extent, and development of subdural hematoma, hyperperfusion syndrome, stroke in magnetic resonance imaging (MRI) and clinical symptoms early within the first 3 months after STA–MCA bypass surgery performed by one neurosurgeon (FD) in a single German institution. Between January 1st, 2015 and March 9th, 2017, all 45 consecutive patients with MMA and hemodynamic insufficiency underwent 64 STA–MCA bypass surgical interventions due to hemodynamic insufficiency. All patients routinely underwent cranial computer tomography on the first day after surgery and MRI of the brain at day 6 after surgery. The MRI protocol included axial fluid-attenuated inversion recovery (FLAIR) sequences, axial T1-weighted, axial diffusion-weighted, and susceptibility-weighted images as well as intracranial time-of-flight (TOF) MR angiography. In addition, a clinical follow-up with another MRI of the brain was performed about 3 months after bypass surgery. In cases with subdural hematoma detected on the routine computer tomography (CT) scan or MRI, the extent was measured in the position of the largest diameter. In all patients, antiplatelet therapy was discontinued 7 days before bypass surgery. Due to the assumption that early restart of antiplatelet therapy after bypass surgery influences the rate of hematoma, we changed the clinical concept between 2015 and 2016 towards longer suspension of antiplatelet therapy. Therefore, retrospectively, it was possible to divide the 64 procedures into two groups. Group 1 resumed their antiplatelet therapy between days 1–3 after surgery. Group 2 resumed their antiplatelet therapy between days 5–7.

In case of bilateral surgery, the second hemisphere was operated after a 3 month waiting period. No patient was operated bilateral simultaneously.

The study was retrospective and the decisions for all procedures and therapy were based on clinical reasoning and not influenced by the study. The study was approved by the local ethics-committee. All patients signed an informed consent. Statistical comparisons were made using Mann–Whitney *U* test (Wilcoxon test). Statistical analysis was performed with SPSS 20 (IBM, Armonk, NY). p values < 0.05 were considered significant.

Results

Participants

Sixty-four procedures were operated using the STA as donor vessel and a distal branch of the MCA as acceptor

vessel in 45 patients. In 48 (75%) procedures, only this direct bypass surgery was performed; in 16 (25%), procedures direct surgery was combined with indirect bypass techniques. The participants were 11 males and 34 females. All participants were adults due to referring bias to our adult Moyamoya center. The age at time of surgery was 41.8 years (age range 18–64, mean, median 43 years, SD 13.68). The great majority (95.5%) of patients were of Caucasian ethnicity (42 Germans, 1 Russian). Only one patient was Arab and one patient was of Asian ethnical origin. The great majority of patients had bilateral MMA ($n=40$, 88.8%), and only five patients were suffering from a unilateral variant.

Postoperative rate and extent of subdural hemorrhage

Within 24 h of surgery, CT scans revealed subdural hematoma in 29 of 64 procedures (45.3%). All subdural hematomas were located at the ipsilateral side to surgery. The mean diameter of these hematomas was 3.9 mm (median 3, SD 2.1, minimum 1 mm, and maximum 10 mm). In eight procedures, a follow-up CT scan was available between the first postoperative day and the MR scan at day 6. In those eight procedures (in 5 cases), the hematoma increased with a mean of 7.6 mm (median 7, SD 4.4, minimum 2 mm, and maximum 12 mm). The MR scan, which was performed at day 6 after surgery (mean 6.01, median six, and SD 4.19), showed subdural hematoma in 38 of 63 procedures (60.3%). The mean diameter of these hematomas in MRI was 5.1 mm (median 4.5 mm and SD 3.4 mm). In 26 of 63 (25.4%) MR scans, there was an increase of the diameter in comparison with the first CT scan at day 1 after surgery with a mean difference of 4.2 mm (median 3 mm and SD 2.9 mm). In 27 MRI scans, the diameter remained stable, and 10 MRI scans revealed an reduced diameter of hematomas with a mean difference of 2.9 mm (median 2.5 mm and SD 2.1). In two patients, an operative decompression was performed (diameter 15 mm in both cases) based on the MRI finding although patients had been asymptomatic. No patient showed epidural hemorrhage.

Antiplatelet therapy

Antiplatelet therapy (aspirin 100 mg per day or clopidogrel 75 mg per day) was prescribed in 63 of 64 procedures before surgery and was stopped 7 days before surgery. This therapy was re-initiated at the first postoperative day after 33 procedures. In 30 procedures (47.6%), the antiplatelet therapy was given at day 5.2 (mean, median 7, SD 2.2) after surgery. In those 33 procedures in which antiplatelet therapy was restarted early at day 1 after surgery, 21 (63.6%) MRI scans showed subdural hematoma. In those 22 procedures, in which antiplatelet therapy was restarted at day 4 or later after surgery (mean day 6.52, median day 7, and SD 1.08) 12 MR scans revealed subdural hematomas. This difference was not significant ($p=0.455$). In the 15 patients with re-initiation at day 7 8 (53.3%) MRI scans showed subdural hematoma. The comparison between the 15 procedures who restarted antiplatelet therapy at day 7 and those 33 procedures who were restarted on antiplatelet therapy at day 1 also revealed no statistically significant difference ($p=0.45$) (Fig. 1).

Early hyperperfusion syndrome in MRI at day 6 after surgery

In the MR scans performed at day 6 FLAIR hyperintensity and diffusion restriction suggesting hyperperfusion were evident after 6 of 64 procedures (9.3%). Three of six (50%) patients had clinical symptoms. Two of these were transient for hours very early after surgery and completely disappeared at day 2 (see Table 1). In all six cases, MRI performed 3 months later showed no abnormality with complete resolution of the hyperintensities.

The six patients with hyperperfusion syndrome did not differ in age (45.33 years mean, median 38 years, SD 18.01) compared to the other 39 patients (40.92 years mean, median 43, SD 13.23; $p=0.725$).

Diffusion-weighted images in MRI at day 6 after surgery

MRI imaging revealed diffusion restriction with typical reduction of ADC map as a sign of ischemia after seven procedures (10.9%) (Fig. 2). Five of these seven patients had no new postoperative symptoms. As shown in Table 1, one patient had paresthesia for seconds, which completely resolved, and one patient had symptoms not related to the area of stroke. All diffusion-restricted areas appeared as little spots suggesting microembolic lesions. In four of these seven patients these diffusion-restricted spots were located in the same hemisphere as surgery, in two patients the other hemisphere was affected and in one patient spots were found in both hemispheres. Six of seven patients were older than 40 years, with a mean age of 46.85 years (median 46.85, SD 1.99). The age of those 38 patient without ischemia was 40.86 (mean, median 39.5, SD 13.91). This difference was not significant (t test, $p=0.266$). Among the group of 7 patients with stroke visible on MRI at day 6, 5 had received antiplatelet therapy early at day 1, and at days 2 and 7, one each. None of the stroke patients smoked in the first 6 days after surgery or had a coagulation disorder.

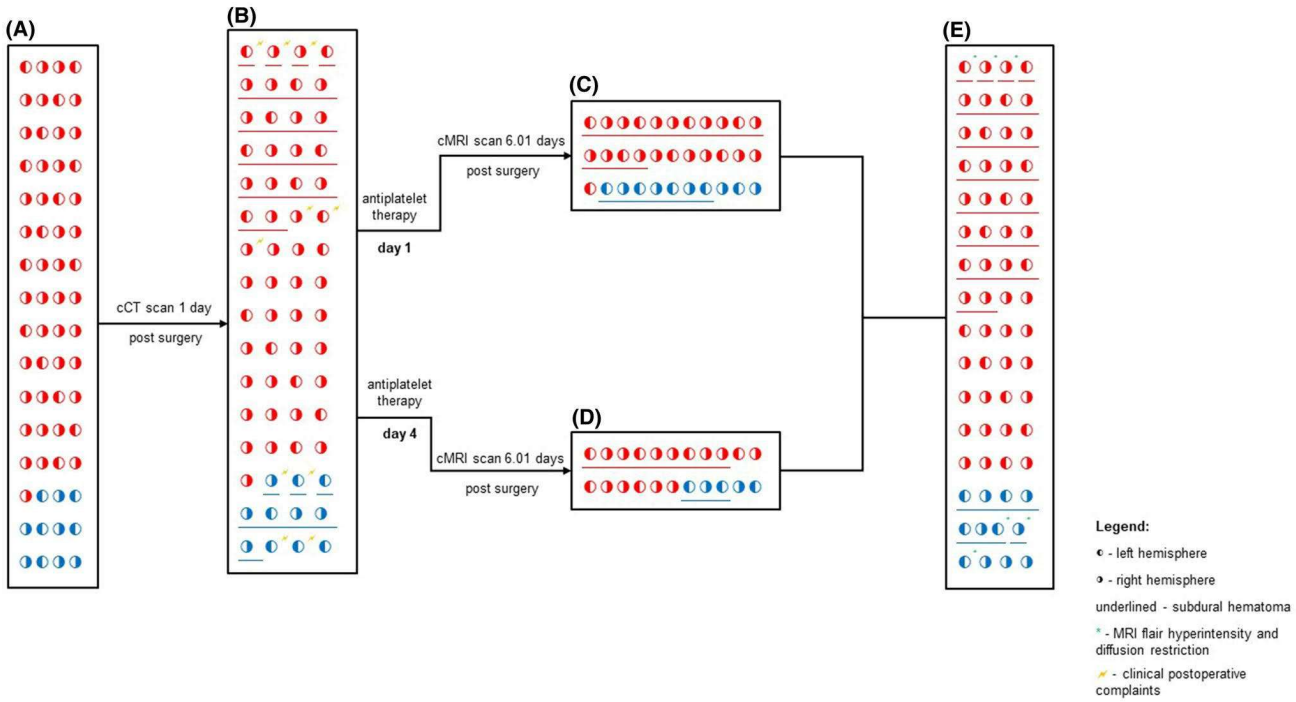

Fig. 1 Recruitment flow chart

Clinical symptoms

Almost all patients suffered from wound pain and headaches during the first days after surgery, which responded to analgesic medication. Therefore, pain was not analyzed as all patients received analgetic drugs on a regular basis. In addition, postoperative soft tissue hematoma and swelling was not analyzed as it was present in all patients and it is hard to quantify.

Altogether, after ten procedures (15%) patients complained of clinical symptoms other than postoperative pain and headaches.

After five procedures (8%) patients reported sensory symptoms in the form of paresthesiae of the fingers and the mouth for seconds during the early days after surgery. These symptoms and the other postoperative complaints are presented in Table 1. After those ten procedures with clinical postoperative complaints, the first CT revealed subdural bleedings in 5 (50%; mean diameter 2.4, median 0.5, SD 2.9), and MRI at day 6 revealed subdural hematoma in additional two (7 of 10, 70%) procedures (mean diameter 4.5, median 4.5, standard 4.7). After those 54 procedures in which patients presented no postoperative complaints, 24 (44.4%) early CT scans revealed postoperative hematoma (mean diameter 3.8 mm, median 3 mm, SD 2.07) and 30 (55.5%) MRI scans showed postoperative subdural hematoma (mean diameter 5 mm, median 4 mm, SD 3.17). The percentage of bleedings in CT ($p = 7.46$) and in MRI ($p = 0.396$) and the diameter of subdural hematoma ($p = 0.07$ for CT, $p = 0.67$ for MRI) did not differ between those patients with or without symptoms.

Early postoperative duplex sonography

After all 64 procedures in all 45 patients extra- and transcranial duplex sonography within the first 6 days revealed bypass patency (100%).

MRI 3 months after surgery

In 63 of 64 procedures, MRI and clinical follow-up were available at 3–4 months after surgery. No new diffusion restrictions occurred during follow-up. Neither ischemias nor bleedings were seen in MRI and all early postoperative findings like subdural hematoma and hyperperfusion syndrome resolved completely (Figs. 3, 4). This included the 36 cases, which showed a subdural hemorrhage on MRI at day 6, and which did not undergo surgical decompression. The spontaneous resolution in all these 36 non-operated cases included also 5 cases who had presented a diameter of hematoma of more than 9 mm (15, 14, 11, 10, and 9 mm, respectively).

Table 1 Clinical characteristics of symptomatic patients

Pat.	Symptom	Duration	Hemorrhage in CT	Hemorrhage in MRI	Hyperperfusion syndrome in MRI	Diffusion-weighted images abnormalities	Further course
F, 27	Prickling contralateral finger and mouth	For seconds within first days Postoperative	No	Yes (2 mm)	No	Yes, embolic character Ipsilateral to surgery	Complete recovery directly
F, 52	Prickling contralateral hand	For seconds within first days Postoperative	No	Yes (1 mm)	No	No	Complete recovery directly
M, 25	Prickling contralateral hand	For seconds within first days Postoperative	Yes (6 mm)	Yes (6 mm)	No	No	Complete recovery directly
F, 21	Prickling contralateral hand	For seconds within first days Postoperative	No	No	No	No	Complete recovery directly
F, 22	Prickling contralateral fingers and mouth	For seconds within first days Postoperative	No	No	No	No	Complete recovery directly
F, 43	Focal motor seizure	For seconds within first days Postoperative	Yes (13 mm)	Yes (15 mm)	No	No	Complete recovery, but burr holes surgery
M, 66	Generalized seizure with postictal aphasia	For minutes within first days Postoperative, aphasia for months	No	No	Yes	Yes, embolic character, not in area for aphasia Contralateral to surgery	Aphasia for months
F, 54	Focal motor seizure	For seconds within first days Postoperative	Yes (3 mm)	Yes (9 mm)	No	No	Complete recovery directly
F, 39	Aphasia and paresis contralateral side	At the day of surgery for hours	Yes (3 mm)	Yes (3 mm)	Yes	No	Complete recovery next day
M, 30	Anarthria	At the day of surgery for hours	Yes (5 mm)	Yes (11 mm)	Yes	No	Complete recovery next day

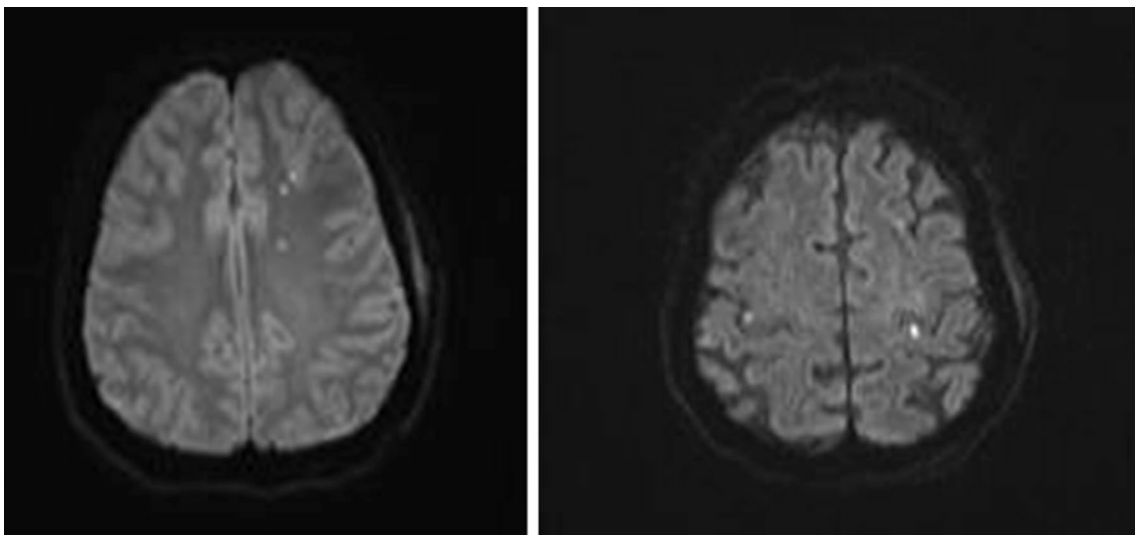

Fig. 2 Embolic stroke in diffusion-weighted MRI (both MRIs if different patients) at day 6 after surgery

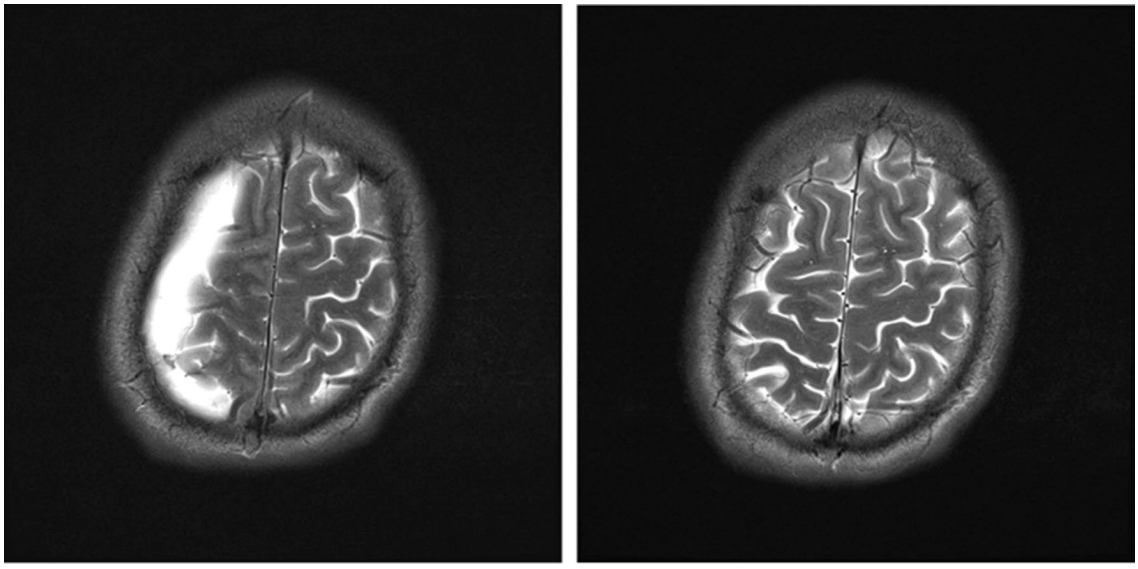

Fig. 3 Subdural hemorrhage (left) at day 6 after surgery and spontaneous recovery (right) after 3 months in MRI (FLAIR sequences)

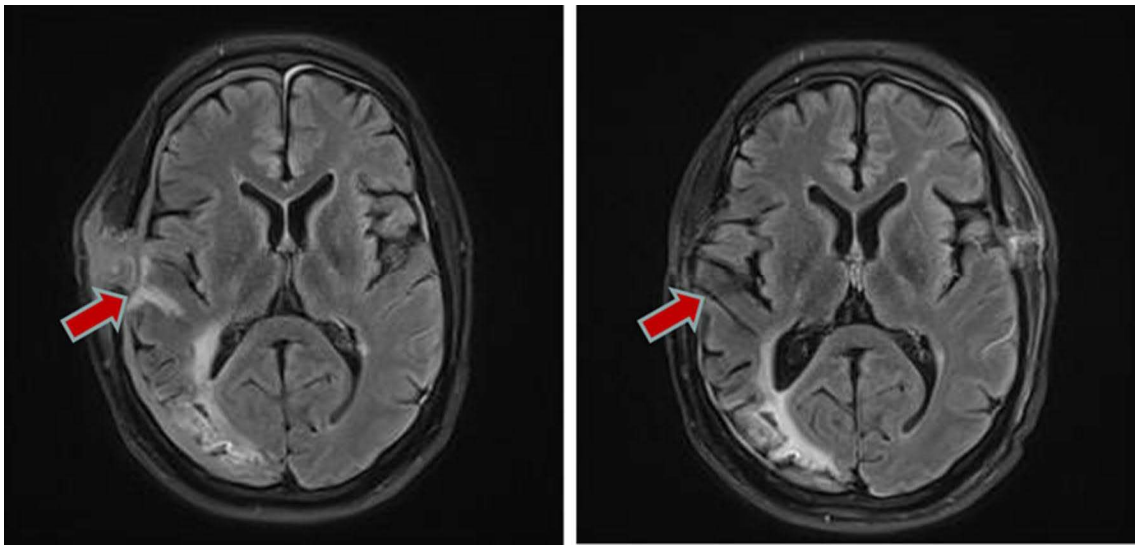

Fig. 4 Hyperperfusion syndrome in FLAIR images in MRI (left) at day 6 after surgery and spontaneous recovery (right) after 3 months

Clinical symptoms 3 months after surgery

In 62 of 63 procedures (98.4%), patients reported no persisting clinical deficit after surgery within 3 months. One patient was lost to clinical follow-up due to living in Kuwait. After one procedure (1.5%), a persisting worsening of aphasia was reported without a new MRI lesion in comparison with the preoperative MRI. This worsening was interpreted as a postictal phenomenon due to a prior generalized seizure and residual aphasia (see Table 1). After three procedures (4.6%), patients reported wound healing complications. These included wound dehiscence and incomplete necrosis, but resolved with appropriate treatment at the 3 month follow-up.

Duplex sonography 3 months after surgery

Extra- and intracranial duplex sonography 3 months after surgery revealed bypass patency in all 44 patients after a total of 63 procedures (100%).

Discussion

This is the first study addressing systematically clinical symptoms, development of subdural hematomas and ischemias in mainly Caucasian European patients with MMA within the first 3 months after STA–MCA surgery. Yu et al. reported in 2016 that no systematic study on complications after bypass surgery is available and summarized the complications in a review article [13].

The literature about revascularisation surgery especially in European Caucasians is sparse and clinically relevant questions are still unsolved.

Recently, the Berlin group addressed perioperative risks of 37 patients with MMA and found eight ischemic complications (11%) [19]. Other studies from European neurosurgical groups focused on angiographic patency, hemodynamic outcomes or had a mainly neurosurgical focus [20–27]. Other experiences from France, Italy, and Germany are mainly based on literature review [10], case series, or small cohorts [28–31].

North American studies addressing the perioperative outcome are based on more ethnically mixed cohorts than typically found in Europe and are, therefore, difficult to compare [32, 33].

Despite the reported low risk, European neurologists are still often reluctant to indicate bypass surgery presumably out of fear of a complicated postoperative course or a low benefit.

Thus, this study was intended to address open questions from a clinical neurologist's point of view. Important points were the analysis of the effect of antiplatelet drugs on the risk of hematoma and to elucidate if seizures and other clinical symptoms are related to hyperperfusion syndrome or bleedings.

For the first time, we demonstrated a high incidence of subdural hematoma (60.3%) early after STA–MCA bypass surgery.

Almost all of these subdural hematomas resolved spontaneously. It is remarkable that also subdural hematomas larger than 9 mm in diameter disappeared during the 3 month follow-up completely. Patients with or without symptoms did not differ in percentage and diameter of subdural hemorrhage. Even patients with extended hemorrhages remained free from symptoms. There was no significant difference concerning percentage and diameter of subdural hematoma between patients with or without early restart of aspirin or clopidogrel. However, we have to acknowledge that possibly, the size of the cohort was too small to rule out an effect of antiplatelet therapy on subdural hematoma. The review by Yu et al. only briefs comments on subdural hematoma [13]. Andoh et al. reported three patients who postoperatively developed chronic subdural hematoma. It was suspected that a preexisting brain atrophy might play a role [18]. In our experience, ipsilateral subdural hematoma is a common (60.4%) but benign complication of bypass surgery.

Based on our findings, we suggest deciding if antiplatelet therapy should be restarted based on an early CT scan performed at day 1 after surgery. The question if the risk of hematoma outweighs the benefit of preventing early embolic strokes when considering an early restart of antiplatelet therapy is not an easy one. Due to the small number of diffusion-restricted spots, the benefit of stroke prevention should be interpreted with caution. However, from a pathophysiological point of view, we believe that longer discontinuation of antiplatelet therapy could increase the risk of embolic stroke in MMA. At the same time, our data suggest that an early resumption of antiplatelet therapy does not seem to increase the risk of clinically relevant complications due to subdural hematoma. This is supported by a study from Schubert et al. with 158 patients and 168 operated hemispheres demonstrating that antiplatelet therapy was not associated with an elevated risk of hemorrhage or need for revision surgery [34]. However, the data do not allow predicting which patient will develop stroke. Age was not a significant discriminator, although six of seven patients were older than 40 years. Kazumata et al. addressed the question of postoperative ischemia in 2014. They evaluated 236 patients and 358 operations. Postoperative ischemia was detected in 4.1% of patients. The risk was higher in adult patients compared to pediatric patients (7.9% per surgery) [16].

Hyperperfusion syndrome following direct bypass surgery has frequently been described in Asian patients [14]. The sudden increase in cerebral blood flow combined with impaired cerebrovascular autoregulation may be the pathomechanism underlying this phenomenon. Incidences between 18 and 50% were described in the Asian literature [35]. It is recommended to lower blood pressure as a preventative measure [13].

Interestingly, our cases diagnosed with hyperperfusion syndrome on MRI, did not differ clinically from patients without these MRI findings.

Only few studies have described clinical symptoms as complication of bypass surgery. With regard to postoperative seizures, Jin et al. analyzed 43 patients with 53 operations, including both indirect and direct bypass procedures [17]. They found postoperative seizures in 10 of 53 hemispheres (18.9%) [17]. A Japanese study by Narisawa et al. analyzed postoperative and suspected a link between seizures and increase in CBF. Forty-four patients with 64 operated hemispheres were included in the study of whom three presented with postoperative seizures within 1–10 days after surgery [36]. The clinical question whether transient paresthesia periorally and in the hands without motor abnormalities represent focal seizures or

should be summarized as a "cheiro-oral syndrome" has not been discussed in depth. Sasamori et al. found in 8 of 35 operated hemispheres (22.9%) such transient paresthesia and interpreted this as a transient "cheiro-oral syndrome". Whether this phenomenon should be interpreted as a focal Jacksonian seizure is relevant, as this would result in a driving ban, in Germany for at least 1 year. On the other hand, we have not considered these transient sensory symptoms as an indication for antiepileptic drug treatment in most cases.

Only one patient reported persistent aphasia accentuated after surgery. However, at the 3 month clinical follow-up, 3 T MRI revealed no new structural lesions. Therefore, we interpreted the accentuation of the aphasia as a possible postictal phenomenon.

Wound healing complications occurred in 3 of 64 procedures (4.6%) compared to a frequency of 21.4% reported previously in the literature [37]. A reason for this good result may be that an one STA—instead of double-type-STA procedure was used necessitating only a small burr hole.

In conclusion, our study provides a detailed description of the early postoperative complications in dominantly Caucasian (95.5%) patients with MMA after revascularizing surgery in a single German institution. Clinically relevant complications were extremely rare with 98% wellbeing 3 months after surgery. Despite the excellent prognosis, this study elucidates that subdural hematoma is a common radiological finding after surgery (60.3%). Interestingly, subdural hematomas, hyperperfusion syndrome, and ischemias in general were subclinical and only evident in high-resolution MRI. The good spontaneous prognosis of postoperative subdural hematomas and other complications should not hide the fact that preoperative patient information should include the small but evident risk of serious complications.

Clearly, an interdisciplinary approach is advised and referral of Moyamoya patients to specialized centers is recommended as it is a rare disease in Europe [10].

To achieve a better data basis for indications to bypass surgery, future studies have to clarify the long-term prognosis regarding new strokes and hemorrhages in Caucasian Europeans.

Conclusion

This study shows excellent prognosis after 3 months after surgery. The indication for revascularization surgery should be based on hemodynamic insufficiency.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical standards This study was approved by local ethics-committee.

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