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BRIEF REPORT

Tyrosine supplementation with high-protein diet as a therapeutic strategy for *YARS1* deficiency

Luisa Averdunk[1,2,*], Karin Konzett[3], Hanna Mandel[4], Tobias Linden[5], Julien Neveu[6], Pierre Rohrlich[7], Melanie Herrmann[8,2], Thomas Lücke[8,2], Sabine Hoffjan[9], Pedro Arsenio Nunez Duran[1,2], Nadra Nasser Samra[4], Sabine Rudnik[10], Desiree E.C. Smith[11], Ertan Mayatepek[1,2], Gajja S. Salomons[11], Felix Distelmaier[1,2,12], Marisa I. Mendes[11]

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ABSTRACT

Purpose: Biallelic pathogenic variants in *YARS1* cause tyrosyl-tRNA synthase (TyrRS) deficiency that compromises the loading of tyrosine to its tRNA. *YARS1* deficiency is characterized by impairment of neurological development, growth, liver function, and hematopoiesis. For other aminoacyl-tRNA synthetase deficiencies, supplementation of the respective amino acid and high-protein diet improved outcome. Whether tyrosine supplementation is effective in *YARS1* deficiency is not known.

Methods: Nine individuals with *YARS1* deficiency received tyrosine (7 with and 2 without a high-protein diet). Aminoacylation was measured in patient-derived fibroblasts.

Results: Since supplementation, cooperation, endurance, and motor skills improved in 8 of 9 children. Two children demonstrated significant progress in active language skills. Weight gain improved in 6 of 9, and vomiting stopped in all cases. In 4 of 9 children, hematological parameters improved. In vitro, the TyrRS activity determined in 3 fibroblast cell lines homozygous for p.(Arg367Trp) was significantly reduced (0%, 6%, and 24%) at 100 μM tyrosine (physiological blood concentration). At 500 μM tyrosine, TyrRS activity increased to almost normal activity relative to controls at 100 μM.

Conclusion: Given the positive cost/risk-benefit ratio, we advocate therapeutic trials with tyrosine supplementation and high-protein diet for *YARS1* deficiency. Further studies should aim to determine variant-specific differences and long-term outcomes in comparison with natural history.

Felix Distelmaier and Marisa I. Mendes contributed equally as last authors to this work.

*Correspondence and requests for materials should be addressed to Luisa Averdunk, Department of General Pediatrics, Neonatology and Pediatric Cardiology, University Children's Hospital, Heinrich-Heine-University, Moorenstraße 5, 40225 Düsseldorf, Germany. *Email address:* luisasusan.averdunk@med.uni-duesseldorf.de; luisa.aver@gmail.com

Affiliations are at the end of the document.

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Introduction

To enter the protein translation machinery, amino acids must be loaded to its cognate tRNA by aminoacyl-tRNA synthetases. In the cytosol, tyrosine is coupled by the tyrosyl-tRNA synthetase (TyrRS), encoded by *YARS1* (HGNC:12840). Biallelic pathogenic variants in *YARS1* impair the loading of tyrosine to its tRNA. As TyrRS plays a crucial role in protein biosynthesis, its deficiency can affect multiple organs including the brain, overall growth, vision and hearing, the liver, hematopoietic system, pancreas, kidneys, endocrinological organs, and lungs.[1] The severity of the disease varies according to different pathogenic variants in *YARS1*. Individuals with the common NM_003680.4:c.1099C>T, p.(Arg367Trp) (NC_000001.11:g.32781089G>A) variant present a milder phenotype, with liver disease showing stabilization during early childhood in most cases. Other variants have been associated with a more severe disease and higher mortality, especially in the first years of life.[2] Prompted by observations of aggravation of symptoms during periods of high protein demand in the early years of life and during infections, others have tested supplementation with a specific amino acid and high-protein diet to treat *MARS1* (HGNC:6898), *IARS1* (HGNC:5330), *LARS1* (HGNC:6512), *FARSB* (HGNC:17800), *KARS1* (HGNC:6215), and *SARS1* (HGNC:10537) deficiency. The approach resulted in an improved outcome.[3-7] Tyrosine supplementation as a therapeutic strategy for *YARS1* deficiency has only been reported in 1 severely affected infant after premature birth (29 weeks of gestation).[8] When tyrosine supplementation was started, the patient was already in a final stage of disease. Tyrosine supplementation did not rescue the end-stage liver and lung failure, and the patient died at 23 months.

Whether tyrosine supplementation might alleviate clinical symptoms of individuals with milder *YARS1* deficiency has not been reported. In this study, we followed 9 *YARS1*-deficient individuals who received tyrosine supplementation with or without high-protein diet for 1 to 2.5 years as a compassionate treatment attempt.

Materials and Methods

Medical treatment

Patients whose legal guardian consented to the compassionate use treatment, received tyrosine. If the families agreed, in addition, a high-protein diet was started.

Patients P1-7 had the common homozygous p.(Arg367Trp) variant. P8 was compound heterozygous for the variants p.(Arg367Trp) and NM_003680.4:c.1571G>T, p.(Gly524Val) (NC_000001.11:g.32775997C>A); P9 was compound heterozygous for NM_003680.4:c.176T>C, p.(Ile59Thr) (NC_000001.11:g.32810939A > G) and NM_003680.4:c.181G>A, p.(Asp61Asn) (NC_000001.11:g.32810934C>T). All individuals received tyrosine with a starting dose of 35 mg/kg/day, gradually increased to 100 to 160 mg/kg/day in 3 doses per day for 1 to 2.5 years. Comparable tyrosine doses have been safely administered for other diseases with no side effects.[9-11] In addition, all participants except for P3 + P4 received high protein diet (2-3 g/kg/day). Metabolic crisis or deterioration triggered by febrile infection is not typical for *YARS1* deficiency. Therefore, no special measures were undertaken during infections. The patients were screened for potential adverse reactions every 3 months (Supplemental Table 1).

Fibroblast studies

Fibroblasts were available from P1+P2+P5 with the homozygous p.(Arg367Trp) variant and from P9 with the compound heterozygous variants p.(Ile59Thr), p.(Asp61Asn). Cells were grown DMEM (0.530 mM tyrosine) with 10% FBS and 1% penicillin-streptomycin. Aminoacylation was measured in fibroblast lysates incubated in reaction buffer (with 100, 250 and 500 µM, as described before.[12] For details, please see supplemental text.

Results

Patient treatment

Blood tyrosine levels (nonfasting) during tyrosine supplementation varied (median 135 µM, range 58-261 µM) and were mostly within or slightly above the normal reference range (Supplemental Figure 1A).

All patients had a history of poor linear growth and weight gain, microcephaly, microcytic anemia and stable liver disease, muscular hypotonia, and intellectual disability.

P1 was an 18-year-old male. Since tyrosine supplementation and high-protein diet began 2.5 years ago, intermittent nausea resolved, and he slightly gained weight (−6.05 to −5.26 z) (Figure 1, Supplemental Table 2). He became more active, energetic, and more engaged in social interaction. According to professionals at school and to therapists, he started to follow demands and to understand questions. According to occupational and physical therapists, his movements became faster and more fluent, and his fine motors skills improved. The reduced intraepidermal nerve fiber density in a skin biopsy from the lower leg, indicative of small fiber neuropathy improved (4.1/mm to 7.0/mm), and compound muscle action potential amplitudes of tibial nerve increased. His beard started to grow.

P2 was a 12-year-old boy, brother of P1. Under treatment for 2.5 years, teachers reported improved attention, concentration, motivation, fine motor skills, and accelerated language development (instead of 2-word-sentences, and he now formed 3-4 word sentences and displayed improved grammar and pronunciation). The therapist noted a significant improvement of

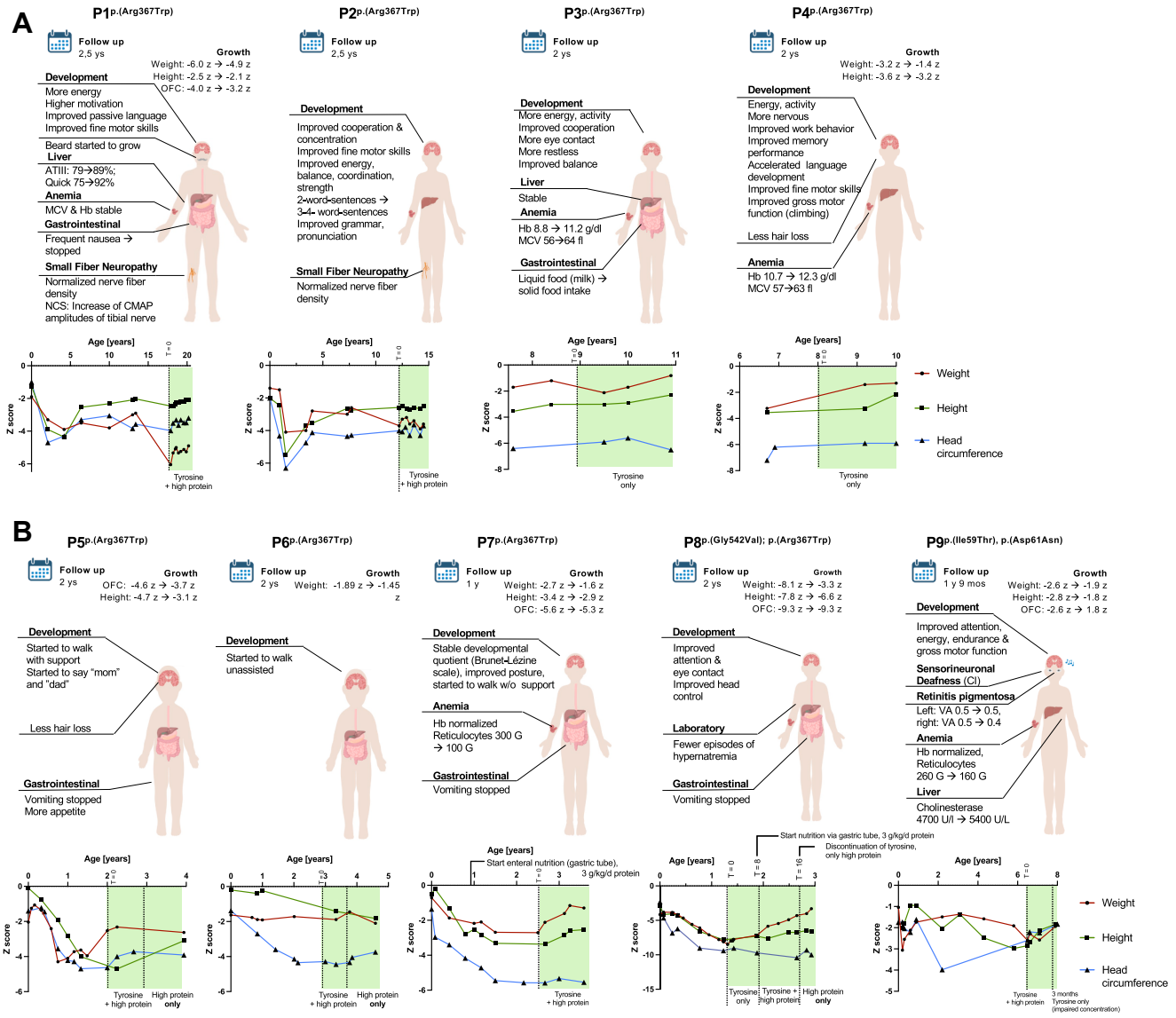

Figure 1 Summary of treatment effects of individuals P1-P4 (Part A) and P5-9 (Part B) All children received tyrosine supplementation with or without a high-protein diet (as indicated in the growth charts). The involved organs and organ systems are highlighted, and the improvements are described. Growth charts visualize the development of *z*-scores before and since treatment. Growth charts of P3 and P4 are only available since migration to the new country. ATIII, antithrombin III; CMAP, combined muscle action potential; Hb, hemoglobin; MCV, mean corpuscular volume; NCS, Nerve conduction studies; OFC, occipitofrontal circumference; VA, visual acuity.

endurance, balance, and strength (Supplemental Table 3). Similar to that in P1, the intraepidermal nerve density fiber improved (7.4/mm to 10.2/mm).

P3 was a 9-year-old boy with autistic behavior. Before the treatment, he had only drunk milk. When tyrosine supplementation without protein fortification was started 2 years ago, he started to eat solid food. According to the teachers, he started to follow simple commands, to anticipate courses of action and began to imitate behavior more often. Teachers also reported an increase of eye contact, improved balance and reduced fear of climbing. Although he showed less self-stimulating behavior, he was more active, restless, and aggressive. Hematological parameters improved.

P4 was an 8-year-old girl, the sister of P3. She was diagnosed with an autism-spectrum disorder. Since tyrosine supplementation, she became more active but also more nervous. According to her teachers and speech therapist, she became more energetic and focused, showed an improved work behavior and memory performance, as well as accelerated language development (broader vocabulary, new: 3-word-sentences). The teachers also reported a significant improvement of fine motor skills. She started climbing on bars and jumping from mats. Loss of hair decreased, and hematological parameters improved.

P5 was a 2-year-old boy with recurrent hospitalizations due to vomiting and diarrhea during his first 1.5 years of

life. After introducing tyrosine 2 years ago, his appetite improved remarkably, vomiting stopped, and frequency of hospitalizations dramatically decreased. His head circumference grew faster, and his height improved. He started to get up to standing position and to walk around with support. He started to say "dad" and "mom." Unfortunately, tyrosine was stopped after 8 months because of irregular supply (due to the war in Israel), but the high-protein diet was continued.

P6 was a 2-year-and-10 month-old male cousin of P5. Since the treatment began 2 years ago, he started to walk on broad base, without assistance. His hair loss stopped. Unfortunately, tyrosine was stopped after 8 months, but the high-protein diet was continued. P7 was 2.5-year-old girl. She had recurrent vomiting and was fed via gastric tube since the age of 11 months. Shortly after tyrosine supplementation was started 1 year ago, the frequency of vomiting significantly decreased. She learned to walk independently.

Body weight and height improved. Anemia improved with normalization of hemoglobin level and reticulocytes. When the therapy was started, her developmental level corresponded to an 8.5-months-old infant. The developmental quotient measured by Brunet-Lézine scale remained stable (0.28 to 0.27) (Supplemental Table 4): the domains posture (0.31 to 0.36) and sociability (0.20 to 0.22) slightly improved and the domains eye-hand coordination (0.31 to 0.26) and language (0.23 to 0.21) slightly deteriorated.

P8 was a 2-year-old girl with severe failure to thrive (weight −8.5 z), severe muscular hypotonia, poor eye contact with nystagmus, hepatopathy, recurrent episodes of vomiting and aspiration pneumonia with bacteremia, dehydration with hypernatremia, and hypoglycemia. In addition, she had ichthyosis caused by a pathogenic variant in *FLG*. Since starting treatment with tyrosine without protein fortification two years ago, she started to gain weight, and vomiting decreased. Eight months later, the gastric tube was placed, and a high-protein diet was started. She had significantly fewer episodes of infections and hypernatremia or hypoglycemia requiring treatment. Attention and eye contact improved. Eight months later tyrosine was discontinued, whereas the high-protein diet was continued. She continued making developmental progress: her head control improved, and she learned the prone position on forearms. However, the frequency of infections and vomiting increased, and episodes of dehydration with hypernatremia restarted.

P9 was a 6.5-year old boy. In addition to poor linear growth and intellectual disability, he had retinitis pigmentosa and sensory neuronal deafness with cochlea implantation 4 years before treatment was started. He had 1 epileptic seizure before starting the tyrosine treatment and 1 since treatment. Since anticonvulsive treatment with lamotrigine, there was no more event. Under treatment with tyrosine and a high-protein diet for 1 year and 9 months, his weight, height, head circumference, and hematological parameters improved. He was more attentive at school; however, his intellectual quotient measured by SON-R decreased during treatment (before: IQ 70, after 16 months: IQ 55). Retinitis pigmentosa was diagnosed 6 months after starting tyrosine. After 1 year of treatment, the visual acuity of the left eye remained stable (0.5 to 0.5), whereas the acuity of the right eye slightly deteriorated (0.5 to 0.4). He was more energetic and had improved endurance when performing exercises with therapists or when walking and climbing. According to his parents and teachers, his muscle strength and balance improved (eg, climbing stairs using both legs individually). Because the parents were interested to find out whether these effects were due to tyrosine or a protein diet, they decided to withdraw tyrosine (cessation attempt). During 4 months of cessation of tyrosine, the teachers reported a reduced attention at school; therefore, tyrosine was restarted.

Liver disease was stable in all cases. As a potential indirect marker of liver disease, we observed increased levels of amino acids that are typically elevated in liver cirrhosis (eg, threonine and proline).[13] Interestingly, threonine and proline showed a trend toward normalization since tyrosine supplementation in most participants (Supplemental Figure 1B and C).

The treatment was well tolerated. Apart from restlessness in P3 and P4 there were no adverse events.

Aminoacylation activity in patient-derived fibroblasts

To explore the effect of tyrosine supplementation in vitro, we measured TyrRS activity in fibroblasts at different tyrosine concentrations.

At 100 μM tyrosine (normal concentration in blood), the TyrRS aminoacylation activity in patient-derived fibroblasts from individuals P1+P2+P5 homozygous for p.(Arg367Trp) was strongly decreased (0%, 6%, and 24% of control). In contrast, the TyrRS activity in fibroblasts from P9 was similar to controls (Figure 2). Histidyl-tRNA-synthetase activity, measured simultaneously, was comparable to controls.

To test the hypothesis that high concentrations of tyrosine could increase the aminoacylation activity, we measured aminoacylation at supra-physiological concentrations [250 and 500 μM] to mimic supplementation. TyrRS activity of fibroblasts with the p.(Arg367Trp) variant increased significantly to almost control activity levels, especially for P2 and P5, in the presence of 500 μM tyrosine.

Discussion

Amino acid supplementation and high-protein diet has been reported beneficial for single individuals with different ARS deficiencies.[3-7]

Following 7 *YARS1* individuals with the p.(Arg367Trp) variant and 2 individuals with different variants during tyrosine supplementation with or without protein fortification for 1-2.5

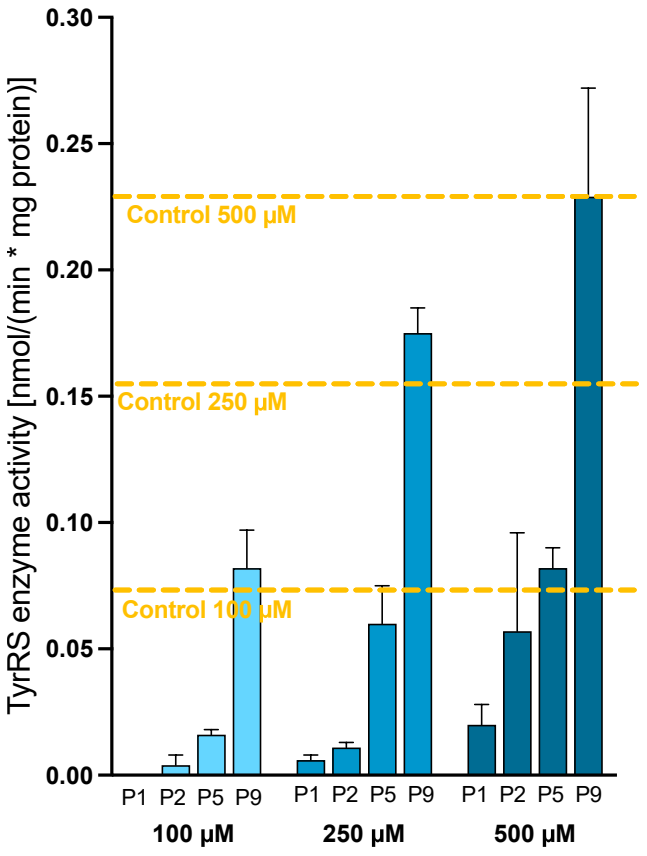

Figure 2 Effect of tyrosine concentration on tyrosyl-tRNA Synthetase (TyrRS) activity in patient-derived fibroblasts. Activity of tyrosyl-tRNA synthetase (TyrRS) in lysates of patient-derived fibroblasts from individuals P1, P2, and P5, homozygous for p.(Arg367Trp), and P9, compound heterozygous for p.(Ile59Thr) and p.(Asp61Asn), compared to controls (yellow dashed line) at 100 µM corresponding to normal tyrosine concentration in blood; and 250 µM and 500 µM, mimicking supra-physiological concentrations during tyrosine supplementation. Aminoacylation activity of P1+P2+P5 is strongly decreased at 100 µM, but increased to almost 100 µM-control activity levels at 250 and 500 µM. The assay was performed in triplicate. Error bars represent standard deviation.

years, we observed improvement of different parameters in all individuals without any significant adverse reaction. Most striking was the improvement of energy and endurance, cooperation, and fine and gross motor skills (all, except for P8). Two children (P2+P4) made significant progress in active language acquisition. In the infants that had recurrent vomiting (P5+P7+P9), vomiting stopped. Six of 9 participants showed improved weight gain (P1+P3+P4+P7+P8+P9). Liver function was stable in all individuals. In 4 individuals (P3+P4+P7+P9) hematological parameters improved.

Our in vitro analyses showed that patient-derived fibroblasts with the p.(Arg367Trp) variant have significantly reduced aminoacylation activity at physiological concentrations. However, at supra-physiological concentrations the aminoacylation activity significantly increased, almost reaching the activity of controls at physiological concentrations. This finding suggests a reduced affinity of mutant TyrRS (p.Arg367Trp) to its substrate tyrosine and an impaired Michaelis-Menten constant K_m that can be partly compensated by high substrate levels. Next to higher substrate availability, another potential mode of mechanism of tyrosine supplementation might be stabilization of variant TyrRS domains by binding of tyrosine. In contrast, enzyme activity of P9 behaved almost similar to controls. This is in line with a less-significant clinical treatment response to tyrosine supplementation and a slightly different clinical phenotype that includes retinitis pigmentosa and deafness, a phenotype that has already been described before.[14] Therefore, the disease mechanism of the compound-heterozygous variants p.(Ile59Thr) and p.(Asp61Asn) likely differs from that of p.(Arg367Trp) and may be related to temperature-sensitive effects on TyrRS activity or to any of the described noncanonical functions of TyrRS, warranting further studies.[3,15-19]

YARS1 deficiency is a rare disease, and long-term natural history data of larger cohorts are not available. Thus, it is difficult to clearly determine the proportion of improvement that is resulting from the treatment. An intentional cessation attempt of tyrosine supplementation with continued high-protein diet was performed in P8 and P9, and a deterioration of some clinical symptoms was observed. The other families wished to continue the tyrosine supplementation given the benefits they witnessed. We observed substantial, sudden, and exponential improvement upon starting with tyrosine supplementation that are unlikely explained by the natural history alone.

Taking into consideration the functional data, the good tolerability, and low costs, we recommend the individualized and compassionate supplementation of tyrosine with high-protein diet as an attempt to improve the outcome of *YARS1* deficiency.

Given the impact of brain development during infancy on later cognitive outcome, we suggest trials with early tyrosine supplementation as a therapeutic strategy for *YARS1* deficiency. Further studies should aim to determine the long-term outcomes, compare these with natural history, and elucidate the role of specific genetic variants in treatment response.

Data Availability

All of the clinical information that has been gathered is included in Supplemental Table 2. If additional details are needed, data will be supplied upon request for purposes of follow-up research studies or personalized patient care. Please send your request to luisa.aver@gmail.com or felix.distelmaier@med.uni-duesseldorf.de.

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Author Contributions

Conceptualization: L.A.; Data Curation (Clinical): L.A., K.K., H.M., T.L., J.N., P.R., S.H., S.R., F.D.; Data Curation (Experimental): M.I.M., G.S.S., D.E.C.S.; Formal Analysis: G.S.S., M.I.M.; Investigation (Clinical): L.A., K.K., H.M., T.L., J.N., P.R., M.H., P.A.N.D.; Investigation (Experimental): M.I.M.; Resources: E.M., G.S.S., N.N.S., L.A.; Visualization: M.I.M., L.A.; Writing-original draft: L.A.; Writing-review and editing: T.L., E.M., K.K., H.M., F.D.

ORCIDs

Luisa Averdunk: http://orcid.org/0000-0003-0719-1607
Karin Konzett: http://orcid.org/0000-0002-8818-9228
Hanna Mandel: http://orcid.org/0000-0002-5230-4247
Pierre Rohrlich: http://orcid.org/0000-0001-8801-4164
Thomas Lücke: http://orcid.org/0000-0001-6875-6582
Sabine Hoffjan: http://orcid.org/0009-0009-6280-1931
Sabine Rudnik: http://orcid.org/0000-0001-8332-0672
Desiree E. C. Smith: http://orcid.org/0000-0003-2053-3392
Ertan Mayatepek: http://orcid.org/0000-0001-8460-3738
Gajja S. Salomons: http://orcid.org/0000-0003-2509-3648
Felix Distelmaier: http://orcid.org/0000-0003-4304-7848
Marisa I Mendes: http://orcid.org/0000-0002-6617-3698

Ethics Declaration

The study was approved by the institutional ethical review board (Heinrich-Heine-University, Düsseldorf, vote #2025-3182-LA & #2021-1340-LA/FD). Legal guardians provided written informed consent for functional studies. The compassionate use treatment was performed as clinical care with patients and parents as partners in care.

The authors have received and archived written consent for participation/publication from every individual whose data are included.

Conflict of Interest

Luisa Averdunk, Ertan Mayatepek, and Felix Distelmaier have in the past attended a scientific conference sponsored by Nutricia (Danone). The conduct of this study was not influenced by any interests related to Nutricia (Danone) or any other company.

Additional Information

The online version of this article (https://doi.org/10.1016/j.gim.2025.101682) contains supplemental material, which is available to authorized users.

Affiliations

[1]Department of General Pediatrics, Neonatology and Pediatric Cardiology, Medical Faculty, University Hospital Düsseldorf, Heinrich-Heine-University, Düsseldorf, Germany; [2]West German Center for Child and Adolescent Health (WZKJ), Germany; [3]Department of Pediatrics, Academic Teaching Hospital, Landeskrankenhaus Feldkirch, Feldkirch, Austria; [4]Institute of Human Genetics and Inherited Metabolic Disorders, Safed, Safed, Israel; [5]University Children's Hospital Oldenburg, Department of Neuropediatrics, Oldenburg, Germany; [6]Service de Neuropédiatrie, Hôpitaux Pédiatriques de Nice, CHU Lenval, Nice, France; [7]Department of Pediatric Hematology-Oncology, Nice University Hospital, Nice, France; [8]St Josef-Hospital, University Children's Hospital, Ruhr-University Bochum, Bochum, Germany; [9]Department of Human Genetics, Ruhr-University Bochum, Germany; [10]Division of Human Genetics, Medical University Innsbruck, Innsbruck, Austria; [11]Department Laboratory Medicine, Laboratory Genetic Metabolic Diseases, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands; [12]MetabERN: European Reference Network for Rare Hereditary Metabolic Disorders, Department of General Pediatrics, Neonatology and Pediatric Cardiology, Medical Faculty, University Hospital Düsseldorf, Heinrich-Heine-University, Düsseldorf, Germany

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