CLINICAL/SCIENTIFIC NOTE OPEN ACCESS

Adult Neuropsychiatric Manifestation of Hartnup Disease With a Novel *SLCA6A19* Variant

A Case Report

Tobias Bachmann, Helene Faust, Rami Abou Jamra, Christina Pott, Michael Kluge, Jost-Julian Rumpf, Florian Then Bergh, and Skadi Beblo

Correspondence
Dr. Beblo
skadi.beblo@medizin.uni-leipzig.de

Neurol Genet 2024;10:e200195. doi:10.1212/NXG.0000000000200195

Abstract

Objectives

In adults, inborn metabolic diseases are often missed in routine diagnostic settings due to a low level of suspicion.

Methods

A patient in their twenties was admitted for an apparent acute exacerbation of anxiety disorder. Medical treatment was unsuccessful, and presumed catatonic psychosis was treated by electroconvulsive treatment. The patient was referred to neurology with reduced level of consciousness, mutism with no targeted movements, obvious anxiety and tetraspasticity, eczema, and reduced body weight.

Results

EEG was normal; repeat brain MRI showed progressive atrophy and leukoencephalopathy. Autoimmune encephalitis was assumed and treated with plasma exchange, high-dose glucocorticoids, and intravenous immunoglobulin. Repeated CSF analyses remained normal. Metabolic workup showed hyperaminociduria, low neutral amino acids, and undetectable tryptophane. Whole-exome sequencing and segregation analysis revealed compound heterozygous, pathogenic and a novel, likely pathogenic variant in the *SLC6A19* gene: c.718C>T, p.(Arg240*) and c.170G>A, p.(Arg57His). Diagnosing Hartnup disease, high-protein diet, and niacin supplementation led to rapid considerable improvement. At 4 months, plasma amino acids were normal; communication and behavior were age-adequate; and spasticity had almost resolved, but polyneuropathy was unchanged.

Discussion

Metabolic workup and whole-exome sequencing are recommended in rapidly progressive neuropsychiatric disease, especially with additional neurologic signs and when standard treatment fails.

Introduction

Tryptophan is an essential amino acid for mammals.[1] It is a precursor for the biosynthesis of coenzymes and neuromodulators, e.g., NAD/NADP(H), kynurenic acid, melatonin, and serotonin.

Nutritional tryptophan deficiency is the cause of pellagra.[2] Initially considered an infectious disease, pellagra has caused substantial mortality due to exclusive corn diet in poor

From the Department of Neurology (T.B., J.-J.R., F.T.B.), University Hospital Leipzig; Institute of Human Genetics (H.F., R.A.J.), University Hospital Leipzig; Department of Psychiatry (C.P., M.K.), University of Leipzig; Hospital for Psychiatry (M.K.), Psychotherapy und Psychosomatics, Klinikum Glauchau; Department of Pediatrics (S.B.), University Hospital Leipzig; and Centre for Rare Diseases (S.B., F.T.B.), University Hospital Leipzig, Germany.

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

The Article Processing Charge was funded by DFG (German Research Foundation): Open access publication funding program.

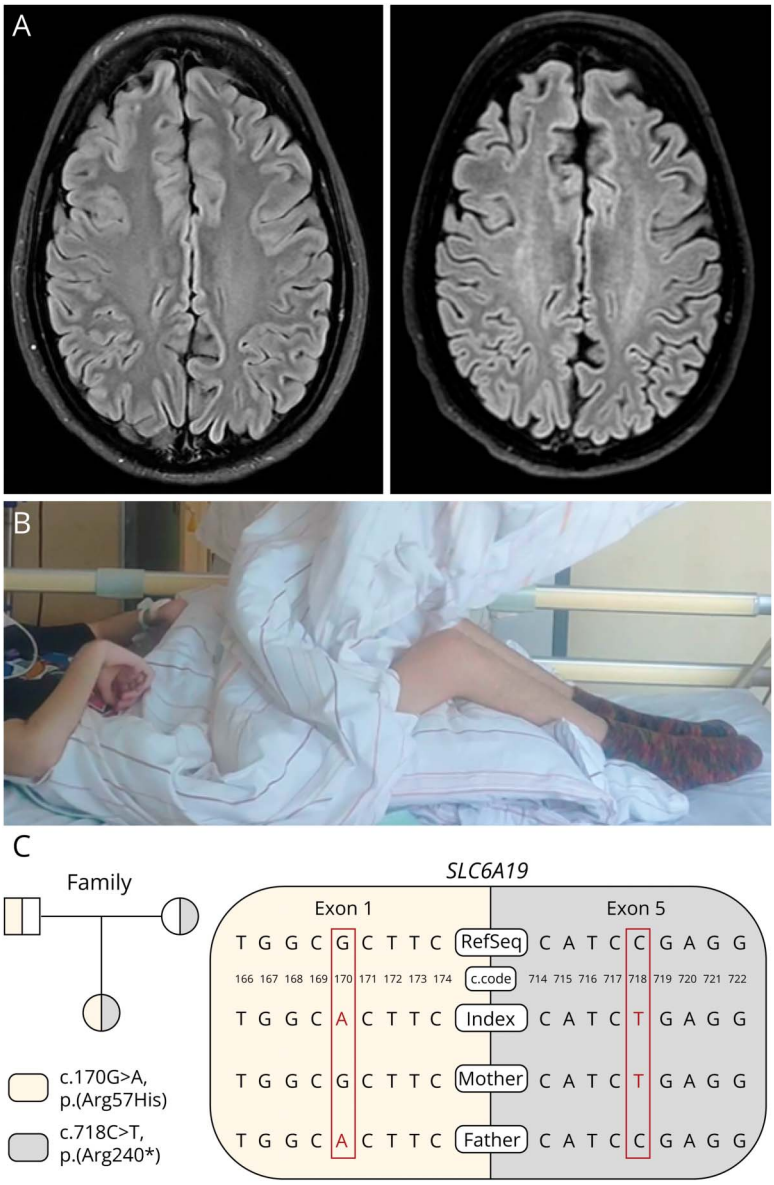
populations. It is characterized by dermatitis, diarrhea, and neuropsychiatric symptoms (depression, psychosis, and dementia).[3]

SLC6A19 is the most important transporter mediating enteral absorption and renal reabsorption of neutral amino acids, including tryptophan. Pathogenic variants of *SLC6A19* cause tryptophan deficiency leading to Hartnup disease, a rare (1:24,000) autosomal-recessive disorder.[2,4,5] Most carriers remain asymptomatic or oligosymptomatic due to a nowadays protein-rich nutrition and the transport of tryptophan included in oligopeptides. However, in situations of inadequate protein supply, patients may develop photosensitive skin lesions and neurologic symptoms.

Case Report

A patient in their twenties, child of nonconsanguineous German parents, had been born after uneventful pregnancy. Psychomotor development was normal. The parents reported a remarkable preference for eating eggs early onwards; a papular rash, especially in sun-lit areas, had been waxing and waning. At 17 years, anxiety disorder was diagnosed, treated with psychotherapy. While on a university exchange program abroad, during a personal crisis, the patient became depressed and agitated, lost weight, returned to Germany, and was eventually admitted to psychiatry. Cranial MRI was normal (Figure, panel A, left). Despite psychotherapy and antidepressant medication, anxiety deteriorated further, weight loss continued. The patient withdrew increasingly, refused food,

Figure Clinical Presentation and Main Investigation Results



Panel A: Cranial MRI 8 weeks before and at the time of diagnosis: rapidly progressive brain atrophy, accompanying leukoencephalopathy, consistent with deteriorated clinical picture. Panel B: aspect of the patient at time of diagnosis: bedridden, typical pellagra-like perioral/facial skin lesions (covered to protect patients' privacy), severe spasticity (arms and legs). Panel C: Molecular genetics. Given are sequences from RefSeq, the patient (index), and their parents. The index carries a pathogenic variant: c.718C>T, p.(Arg240*), inherited maternally, and a likely pathogenic variant: c.170G>A, p.(Arg57His), inherited paternally, in the gene *SLC6A19*, resulting in a compound-heterozygous state.

and within 6 weeks from admission, became bed-ridden; when turning mute and febrile, and creatine kinase rose, pernicious catatonia was assumed, and treated with lorazepam, olanzapine, and eventually electroconvulsive treatment. As patient's clinical course deteriorated, the patient was referred to neurology, with reduced level of consciousness, mutism with no targeted movements, spastic tetraparesis despite diminished deep tendon reflexes, and distal-symmetrical hypalgesia (Figure, panel B); general examination was remarkable for eczema and malnutrition (body mass index 19.0 kg/m^2). EEG was normal; EMG/ENG was consistent with lower motor neuron dysfunction. Repeat brain MRI (8 weeks after initial MRI) showed leukoencephalopathy and progressive brain atrophy (Figure, panel A, right). CSF remained unremarkable, including antibodies associated with autoimmune encephalitis. Still, plasma exchange was initiated, followed by high-dose glucocorticoid and IV immunoglobulin therapy, without improvement. A nasogastric tube was placed, and standard formula diet introduced.

Metabolic Diagnostic Procedures

Dried blood spot analysis for carnitine, acyl-carnitines, and amino acids was normal, as were urinary organic acids. Plasma amino acid profile yielded low concentrations of threonine, leucine, asparagine, and histidine, while tryptophan was undetectable (Table). By contrast, marked hyperaminoaciduria was shown (Table).

Genetics

Whole-exome sequencing of genomic DNA from peripheral blood leucocytes using standard methods revealed 2 variants (confirmed by Sanger sequencing) in the *SLC6A19* gene: c.718C>T, p.(Arg240*) and c.170G > A, p.(Arg57His) (Figure, panel C). We classified the variant c.718C>T as pathogenic and the variant c.170G>A as likely pathogenic according to the ACMG guidelines[6]: the variant c.718C>T leads to a premature stop codon (PVS1), is absent in controls in homozygous state (gnomAD, PM2_SUP), and has been reported twice as pathogenic in databases (PS4_MOD, HGMD: CM042479 and ClinVar variation ID 2020). Segregation analysis confirmed compound-heterozygous state of both variants: the mother carries c.718C>T and the father carries c.170G>A (PM3). The variant c.170G>A is absent in controls in homozygous state (gnomAD, PM2_SUP), in silico predicted to be deleterious (PP3, CADD: 25.5, SIFT, PolyPhen2), and at the same amino acid position, a different amino acid change had been reported as pathogenic (PM5_SUP[4]).

Further Course

We introduced high-protein formula (3 g/kg body weight/d) and supplemented niacin (100 mg bid); IV amino acids were administered to supply 800 mg of tryptophan daily. The patient's condition improved considerably within 1 week to drinking from a cup and eating prepared food, speaking short sentences. Plasma levels of most neutral amino acids rose to the lower normal range. Over 4 weeks, the patient became consistently awake, speaking coherently and referring to conversations held several days ago, although interaction remained child-like. Spasticity resolved, peripheral weakness improved marginally; sitting unassisted and standing assisted for up to 20 minutes became possible. At transfer to a rehabilitation facility, diet included oral food with at least 2 g/kg of protein and niacin 100 mg bid.

Table Plasma and Urinary Amino Acid Profile

Plasma neutral amino acids	Reference range (μmol/L)	At diagnosis	4 wk of treatment	4 mo of treatment	Urinary amino acids (μmol/mol Krea) at diagnosis	After 4 mo of treatment	Reference range
Ala	177–583	283	775	867	1,592	3,301	16–68
Gln	205–756	739	664	743	1,938	4,181	20–76
His	72–124	20	64	69	444	1,152	26–153
Leu	72–201	56	181	281	140	1,954	2–11
Ser	58–181	102	124	138	1,255	1,460	21–50
Trp	10–140	0	33	33	60	164	0
Tyr	34–112	34	52	66	623	870	2–23
Thr	60–255	52	220	212	564	2,138	7–29
Phe	35–85	43	66	68	129	588	2–19
Val	119–336	122	200	295	227	1,828	6–34
HAA/OAASee ref. 15	n.a.	n.a.	n.a.		5.0	7.8	

Abbreviation: HAA/OAA = ratio of Hartnup amino acids to other amino acids in urine.
At diagnosis, marked hyperaminoaciduria despite marked depletion of plasma amino acids and undetectable tryptophan. On treatment, plasma amino acids within the reference range, with even more pronounced hyperaminoaciduria.

Four months after diagnosis, the patient communicated in an adequate way. Muscle tone was only slightly elevated in the legs, and ankle clonus no longer present. Polyneuropathy was largely unchanged with distal weakness and pallhypesthesia. Using the wheeled walker, the patient completed the Timed-up-and-Go Test in 22 seconds ("significant impairment"),[7] and in the Six-Minutes-Walk test, covered 220 m (individual reference would be 739 m[8]). Diet included 94 g protein from high-protein formula, and medication 200 mg niacin/day and gabapentin. Metabolic assessment showed plasma amino acid concentrations within the normal range. As expected, hyperaminoaciduria had even increased (see Table).

Discussion

Healthy adults in central and western Europe consume 1–1.2 g protein/kg body weight daily,[9] providing an average of 12 mg tryptophan/kg, almost 3 times as much as considered necessary.[10] In Hartnup disease, clinical course is often additionally obscured by absorption of tryptophan-containing oligopeptides. In malnutrition, patients with Hartnup may develop shortage of NAD, melatonin, and serotonin. Even without obvious malnutrition, epileptic seizures, autism, and other behavioral abnormalities can occur.[11,12]

In our patient, the mostly "compensated" Hartnup disease may have contributed to behavioral disorder[12] long before the current exacerbation, which was triggered by loss of appetite and anorexia, eventually fulfilled criteria of acute psychosis, and was even diagnosed as pernicious catatonia. Over 2 months, MR imaging documented structural brain damage. Although the course suggested autoimmune encephalitis or a rapidly progressing neurodegenerative disorder, a combination of clinical suspicion, nondiagnostic routine neurologic laboratory investigations, a broad metabolic workup, and whole-exome sequencing eventually unveiled an inborn metabolic disorder. This diagnosis provided the option of dietary treatment and vitamin supplementation, with rapid correction of the metabolic derangements, soon followed by clinical improvement.

Whole-exome sequencing revealed a known pathogenic and a novel variant in *SLC6A19*. Clinical and biochemical results confirm the novel variant as likely pathogenic. We regard this as retrospective phenotyping in the sense of the ACMG guidelines (PP4 [6]), confirming Hartnup disease. This is further underlined by clinical benefit of specific treatment. We assume low residual transport activity, potentially combined with more severely disturbed ependymal amino acid transport,[2] since psychiatric symptoms started in adolescence, and once decompensated our patient showed a very severe course. Available literature reports manifestation of Hartnup disease throughout life, with heterogeneous course. Cases with a mixed (classical pellagra-like) picture have been described, or isolated neurologic[11,13] or psychiatric[12] courses. Such devastating development over a short period, as we observed, has not been reported.

The incidence of Hartnup disease is estimated at around 1: 30,000 live births.[14] Frequency of heterozygosity for the identified variants was 1 (p.(Arg57His)) and 2 (p.(Arg240*)) in 14,370 samples in our in-house database, and were reported 5 times (p.(Arg57His)) and 11 times (p.(Arg240*)) in gnomAD. These figures suggest a higher prevalence than hitherto described: at least 20–30 patients are probably born in Germany every year. Our case demonstrates that a series of unfortunate events can lead to severe disease in a seemingly healthy adult. Treating physicians may not consider an inborn metabolic disorder in such a situation, and some patients may never be recognized. This calls for extending diagnostic procedures to include inborn errors of metabolism (using whole-exome sequencing and generous metabolic workup) in neuropsychiatric disease with unusual age at onset, non-classical clinical characteristics, or lack of treatment response.

Acknowledgment

The authors are grateful for the patient's agreement to have her course and data reported publicly, and her family for supporting communication in this respect.

Study Funding

The authors report no targeted funding.

Disclosure

The authors report no relevant disclosures. Go to Neurology.org/NG for full disclosures.

Publication History

Received by *Neurology: Genetics* March 4, 2024. Accepted in final form August 26, 2024. Submitted and externally peer reviewed. The handling editor was Associate Editor Suman Jayadev, MD.

Appendix Authors

Name	Location	Contribution
Tobias Bachmann	Department of Neurology, University Hospital Leipzig, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Helene Faust	Institute of Human Genetics, University Hospital Leipzig, Germany	Major role in the acquisition of data; analysis or interpretation of data
Rami Abou Jamra	Institute of Human Genetics, University Hospital Leipzig, Germany	Major role in the acquisition of data; analysis or interpretation of data
Christina Pott	Department of Psychiatry, University of Leipzig, Germany	Major role in the acquisition of data
Michael Kluge	Department of Psychiatry, University Hospital Leipzig; Hospital for Psychiatry, Psychotherapy und Psychosomatics, Klinikum Glauchau, Germany	Major role in the acquisition of data

Continued

Appendix *(continued)*

Name	Location	Contribution
Jost-Julian Rumpf	Department of Neurology, University Hospital Leipzig, Germany	Major role in the acquisition of data; analysis or interpretation of data
Florian Then Bergh	Department of Neurology, University Hospital Leipzig; Centre for Rare Diseases, University Hospital Leipzig, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Skadi Beblo	Department of Pediatrics, University Hospital Leipzig; Centre for Rare Diseases, University Hospital Leipzig, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data

References

1. Parthasarathy A, Cross PJ, Dobson RCJ, Adams LE, Savka MA, Hudson AO. A three-ring circus: metabolism of the three proteogenic aromatic amino acids and their role in the health of plants and animals. *Front Mol Biosci*. 2018;5:29. doi:10.3389/fmolb.2018.00029
2. Kravetz Z, Schmidt-Kastner R. New aspects for the brain in Hartnup disease based on mining of high-resolution cellular mRNA expression data for SLC6A19. *IBRO Neurosci Rep*. 2023;14:393-397. doi:10.1016/j.ibneur.2023.03.010
3. Pitche PT. Pellagre et érythèmes pellagroïdes. *Sante*. 2005;15(3):205-208.
4. Kleta R, Romeo E, Ristic Z, et al. Mutations in SLC6A19, encoding B0AT1, cause Hartnup disorder. *Nat Genet*. 2004;36(9):999-1002. doi:10.1038/ng1405
5. Scriver CR, Mahon B, Levy HL, et al. The Hartnup phenotype: mendelian transport disorder, multifactorial disease. *Am J Hum Genet*. 1987;40(5):401-412.
6. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17(5):405-424. doi:10.1038/gim.2015.30
7. Salarian A, Horak FB, Zampieri C, Carlson-Kuhta P, Nutt JG, Aminian K. iTUG, a sensitive and reliable measure of mobility. *IEEE Trans Neural Syst Rehabil Eng*. 2010;18(3):303-310. doi:10.1109/TNSRE.2010.2047606
8. Enright PL. The six-minute walk test. *Respir Care*. 2003;48(8):783-785.
9. Max-Rubner-Institut. Nationale Verzehrsstudie II. Ergebnisbericht, Teil 2: Die bundesweite Befragung zur Ernährung von Jugendlichen und Erwachsenen [online]. nbn-resolving.org/urn:nbn:de:gbv:ka51-2008091124
10. Klaessens S, Stroobant V, De Plaen E, van den Eynde BJ. Systemic tryptophan homeostasis. *Front Mol Biosci*. 2022;9:897929. doi:10.3389/fmolb.2022.897929
11. Zhu Y, Chen L, He J, et al. Study of seizure-manifested hartnup disorder case induced by novel mutations in SLC6A19. *Open Life Sci*. 2018;13:22-27. doi:10.1515/biol-2018-0003
12. Žigman T, Petković Ramadža D, Šimić G, Barić I. Inborn errors of metabolism associated with autism spectrum disorders: approaches to intervention. *Front Neurosci*. 2021;15:673600. doi:10.3389/fnins.2021.673600
13. Wang X, Li X-Y, Piao Y, et al. Hartnup disease presenting as hereditary spastic paraplegia and severe peripheral neuropathy. *Am J Med Genet. A* 2022;188(1):237-242. doi:10.1002/ajmg.a.62475
14. Orphanet. Hartnup syndrome [online]. orpha.net/consor/cgi-bin/Disease_Search.php?lng=DE&data_id=502&Disease_Disease_Search_diseaseGroup=Hartnup&Disease_Disease_Search_diseaseType=Pat&Krankheite(n)/Krankheitsgruppe=Hartnup-Syndrom&title=Hartnup-Syndrom&search=Disease_Search_Simple. Accessed November 14, 2023.
15. Haijes HA, Prinsen HCMT, de Sain-van der Velden MGM, Verhoeven-Duif NM, van Hasselt PM, Jans JJM. Accurate discrimination of Hartnup disorder from other aminoacidurias using a diagnostic ratio. *Mol Genet Metab Rep*. 2020;22:100551. doi:10.1016/j.ymgmr.2019.100551