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Accurate discrimination of Hartnup disorder from other aminoacidurias using a diagnostic ratio

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ABSTRACT

Introduction: Hartnup disorder is caused by a deficiency of the sodium dependent B^0 AT1 neutral amino acid transporter in the proximal kidney tubules and jejunum. Biochemically, Hartnup disorder is diagnosed via amino acid excretion patterns. However, these patterns can closely resemble amino acid excretion patterns of generalized aminoaciduria, which may induce a risk for misdiagnosis and preclusion from treatment. Here we explore whether calculating a diagnostic ratio could facilitate correct discrimination of Hartnup disorder from other aminoacidurias.

Methods: 27 amino acid excretion patterns from 11 patients with genetically confirmed Hartnup disorder were compared to 68 samples of 16 patients with other aminoacidurias. Amino acid fold changes were calculated by dividing the quantified excretion values over the upper limit of the age-adjusted reference value.

Results: Increased excretion of amino acids is not restricted to amino acids classically related to Hartnup disorder ("Hartnup amino acids", HAA), but also includes many other amino acids, not classically related to Hartnup disorder ("other amino acids", OAA). The fold change ratio of HAA over OAA was 6.1 (range: 2.4–9.6) in the Hartnup cohort, versus 0.2 (range: 0.0–1.6) in the aminoaciduria cohort ($p < .0001$), without any overlap observed between the cohorts.

Discussion: Excretion values of amino acids not classically related to Hartnup disorder are frequently elevated in patients with Hartnup disorder, which may cause misdiagnosis as generalized aminoaciduria and preclusion from vitamin B3 treatment. Calculation of the HAA/OAA ratio improves diagnostic differentiation of Hartnup disorder from other aminoacidurias.

1. Introduction

Aminoacidurias are caused by defective amino acid transport across the renal epithelium. Inborn errors of amino acid transporters include lysinuric protein intolerance (LPI) (MIM #222700), cystinuria (MIM #220100), iminoglycinuria (MIM #242600), dicarboxylic amino aciduria (MIM #222730) and Hartnup disorder (MIM #234500). Next to defective amino acid transporters, transport of amino acids can also be impaired by general dysfunction of the renal tubule, as occurs for example in Fanconi syndrome [5] and Lowe syndrome [8]. Aminoacidurias are biochemically classified according to their specific amino acid excretion pattern.

Hartnup disorder has an estimated frequency of 1:20.000 [9] and is caused by a deficiency of the sodium dependent B^0 AT1 neutral amino acid transporter, encoded by *SLC6A19*. This transporter is mainly expressed in the brush border membrane of the proximal kidney tubules and in the jejunum [7,12,13]. The disorder is biochemically characterized by increased excretion of neutral amino acids including alanine, serine, threonine, valine, leucine, isoleucine, phenylalanine, tyrosine, asparagine, glutamine, tryptophan, histidine and citrulline, whereas excretion of other amino acids is reported to be less affected (Nanto-Salonen et al. 2006, Vademecum Metabolicum).

The impaired renal and intestinal transport of neutral amino acids is a risk factor for developing amino acid deficiencies, tryptophan deficiency in particular. As tryptophan is the precursor for serotonin and nicotinamide, also known as vitamin B3, the clinical symptoms of

Abbreviations: LPI, lysinuric protein intolerance; MIM, Mendelian inheritance in man

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Table 1
Amino acid excretion of patients with Hartnup disorder.

	Upper limits age groups			Patient 1					Patient 2				Patient 3						Patient 4				
				1.1	1.2	1.3	1.4	1.5	2.1	2.2	2.3	2.4	3.1	3.2	3.3	3.4	3.5	3.6	4.1	4.2	4.3	4.4	4.5
Age group	05	06	07	05	05	05	05	05	07	07	07	07	05	05	06	06	06	07	05	05	05	05	06
Alanine	80	85	59	1099	1443	1102	539	969	407	264	472	479	1026	621	1020	968	1041	1108	474	590	585	460	1429
Serine	95	78	69	1471	2015	1220	724	1145	754	536	700	655	1550	1002	1108	1154	997	988	736	745	892	672	1631
Threonine	45	36	48	826	1180	608	556	734	348	325	455	423	891	724	506	550	564	567	513	376	485	374	854
Valine	12	11	7	344	1094	329	381	550	500	560	653	663	605	388	363	338	416	389	441	349	377	243	803
Leucine	12	9	6	98	776		141	281	193	259	287	332	199	220	81	117	151	138	181	67	87	33	189
Isoleucine	7	7	5	155	510		143	262	131	175	197	229	189	168	88	88	115	131	192	105	135	50	199
Phenylalanine	20	17	11	119	353	95	122	156	151	134	161	175	152	128	84	76	96	101	109	95	110	37	123
Tyrosine	42	37	27	623	949	536	432	616	299	233	254	249	717	488	377	431	521	272	375	327	436	231	656
Asparagine	29	27	9	760	972		520	569	317	316	437	357		504	382	417	430	389	388	355	441	312	492
Glutamine	137	98	57	2658	4684	3176	1190	1873	1571	1859	1257	1793	3009	1422	1858	1560	2030	1443	1052	1197	1272	997	879
Histidine	216	184	153	836	1259	732		804	436	424	396	443	58	710	602	656	640	515	489	557	587	477	713
Citrulline	18	5	2	38	134		34	90	54	51	44	53	50	50	23	31	18	14	8	2	1	8	26
Arginine	9	8	7	14	57	8	18	34	11	6	8	8	9	14	9	11	6	6	11	2	5	2	11
Lysine	64	20	52	237	751	154	202	359	67	59	80	103	118	208	57	70	59	57	87	37	40	32	84
Aspartic acid	21	7	5		47		3	4	40	12	15	23	42	42	26	34		18	29	19	26	43	19
Glutamic acid	31	6	3	63	258			73	107	89	178	88	622	622	31	65	12	62	36	20	31	37	35
Glycine	201	252	199	562	739	377	297	488	224	111	169	195	475	365	437	647	718	730	334	309	356	311	877
Cysteine	17	16	19	24	71	22	26	34	65	31	45	46	66	60	28	24	21	20	32	20	26	25	40
Ornithine	7	6	5	5	24	2	4	8	5	6	5	9	9	9	5	7		4	5	2	3	2	6
Taurine	79	79	80	17	100		13	25	13	21	12	32	75	22	475	40	19	22	71	193	78	17	46
α-amino-butyric acid	7	7	7	28	56		43	50	25	38	32	35	54	48	22	35	24	25	44	42	42	23	53

Amino acid excretion patterns of patients with Hartnup disorder in mmol/mmol creatinine. Age group: age adjusted reference values were obtained from literature, taking into account seven age groups: first week (1), first week till first month (2), first month till four months (3), four months till two years (4), two years till ten years (5), ten years till eighteen years (6) and above eighteen years (7) [1]. Hartnup amino acids: alanine to glutamine. Other amino acids: arginine to α-aminobutyric acid.

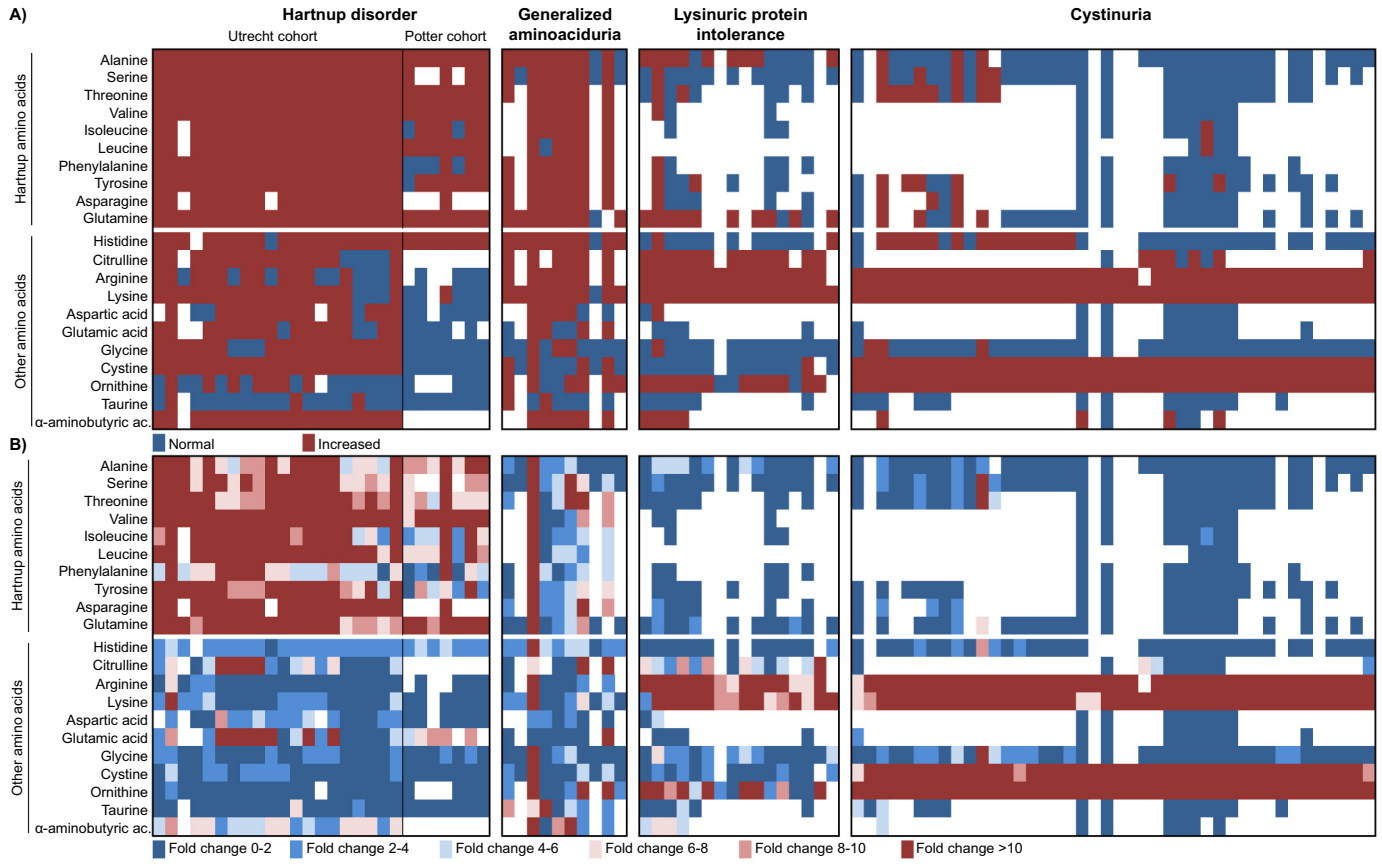

Fig. 1. Visualization of amino acid excretion in Hartnup disorder.
A) Heatmap of amino acid excretion values. Normal excretion values are depicted in blue, and excretion values higher than age-adjusted upper reference values are depicted in red. White indicates that excretion values of that amino acid were not quantified. B) Heatmap of the fold changes of the urinary amino acid concentrations over the age-adjusted upper reference value, allowing visual differentiation of Hartnup disorder from generalized aminoaciduria, lysinuric protein intolerance and cystinuria. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Hartnup disorder are those of a nicotinamide deficiency. Reported symptoms include dermatological symptoms, particularly a pellagra-like rash and light-sensitive dermatitis, intermittent cerebellar ataxia and psychiatric symptoms as emotional instability, delirium and hallucinations [3]. All symptoms respond well to treatment with vitamin B3 [15].

To date, many individuals remain asymptomatic [14], likely because of a sufficiently high intake of protein, tryptophan, vitamin B3 or a combination thereof [3]. However, even in asymptomatic patients, accurate diagnosis of Hartnup disorder is essential [4,14], to ensure correct differentiation of Hartnup disorder from other aminoacidurias, which would demand alternative diagnostic trajectories. Biochemically, Hartnup disorder is diagnosed based on the amino acid excretion profile. Here, we demonstrate that patients with Hartnup disorder may present with an amino acid excretion pattern that closely resembles generalized aminoaciduria [2,3,6]. We show that this potential misdiagnosis can be overcome by quantification, visualization and computation of urinary amino acids, enabling us to correctly discriminate Hartnup disorder from other causes of aminoaciduria.

2. Methods

2.1. Patient inclusion

Twenty-seven urine samples of 11 patients with Hartnup disorder were analyzed. Four of these patients were included at the University Medical Centre Utrecht. Hartnup disorder was confirmed through PCR amplification followed by Sanger sequencing of *SLC6A19*. Patient 1 is compound heterozygous for the pathogenic *SLC6A19* c.517G > A (p.Asp173Asn) and c.1173 + 2T > G (p.?) mutations [13]. Patient 2, 3 and 4 are homozygous for the common *SLC6A19* c.517G > A (p.Asp173Asn) mutation. Patient 3 and 4 are siblings. To extend the Hartnup disorder cohort, amino acid excretion patterns of seven patients with Hartnup disorder previously published by Potter et al. were included [11]. Hartnup disorder was genetically confirmed in these patients by Seow et al. [13]. One patient (patient 2/II) was excluded, because of heterozygosity for cystinuria type II. In the patients from Potter et al., amino acid excretion patterns were quantified using a Beckman 6300 amino acid analyzer [11].

To differentiate Hartnup disorder from other aminoacidurias, 10 samples of 7 patients with generalized aminoaciduria, 16 samples of 2 patients with LPI and 42 samples of 7 patients with cystinuria were included, coming to a combined aminoaciduria cohort of 68 samples of 16 patients, all from the University Medical Centre Utrecht. All diagnoses were genetically confirmed.

2.2. Quantification of amino acid excretion

Amino acid excretion was quantified at the University Medical Centre Utrecht using a Biochrom amino acid analyzer (Isogen Life Sciences, de Meern, the Netherlands) according to diagnostic standards. Amino acid excretion was expressed in mmol/mol creatinine. Age adjusted reference values were obtained from literature, taking into account seven age groups: first week (1), first week till first month (2), first month till four months (3), four months till two years (4), two years till ten years (5), ten years till eighteen years (6) and above

eighteen years (7) [1].

2.3. Statistical analysis

Amino acid fold changes were calculated by dividing the quantified excretion values over the upper limit of the age-adjusted reference value. Amino acids were grouped into Hartnup amino acids (HAA) versus other amino acids (OAA). HAA included alanine, serine, threonine, valine, leucine, isoleucine, phenylalanine, tyrosine, asparagine, glutamine, tryptophan, histidine and citrulline (Nanto-Salonen et al. 2006, Vademecum Metabolicum), and OAA included arginine, lysine, aspartic acid, glutamic acid, glycine, cysteine, methionine, proline, ornithine, taurine and alpha-aminobutyric acid. Statistical analyses were performed using R programming language. Results were visualized in both heatmaps and scatter plots. Data files and R code are available upon request.

3. Results

Amino acid excretion patterns of the patients with Hartnup disorder in the Utrecht cohort are presented in Table 1. This table displays that increased excretion of amino acids is not restricted to HAA, but also includes many OAA, including cystine (in all 20 samples), alpha-aminobutyric acid (in 19/20), glycine and lysine (both in 17/20), citrulline and glutamic acid (both in 15/20), aspartic acid (in 14/20) and arginine (in 12/20). This precludes discrimination of Hartnup disorder from other aminoacidurias and induces the risk of misclassification as generalized aminoaciduria (Fig. 1A).

We assessed whether the degree of increase could aid differentiation of Hartnup disorder from other aminoacidurias. Indeed, quantification of amino acid excretion values and computation of amino acid fold changes enabled visual discrimination between Hartnup disorder and generalized aminoaciduria (Fig. 1B). The heatmap demonstrating the fold changes shows that, unlike in patients with generalized aminoaciduria, in both Hartnup disorder cohorts the fold changes of HAA were strikingly higher than the fold changes of OAA. LPI and cystinuria could also be recognized easily: LPI based on clear increases of arginine, lysine and ornithine and cystinuria based on the additional increase of cystine (Fig. 1B).

In patients with Hartnup disorder, the mean fold change of HAA ranged from 8.1 for phenylalanine to even 49.7 for valine. Histidine, an amino acid classically related to Hartnup disorder, was unexpectedly only slightly elevated, with a mean fold change of 3.1. Surprisingly, this was even lower than in generalized aminoaciduria, for which a mean fold change of 7.8 was calculated. Histidine excretion, while increased in 18/20 samples, seemed similar to the excretion of OAA (range mean fold change 0.9–13.1). Computation of the ratio of the mean fold change of HAA over OAA (including histidine) clearly distinguished Hartnup disorder from other aminoacidurias (Table 2, Fig. 2A). The mean HAA/OAA ratio in the Hartnup cohort was 6.1, whereas the mean HAA/OAA ratio in the aminoaciduria cohort was only 0.2 (Mann-Whitney test $p < .0001$). Moreover, no overlap was observed between the two cohorts, as the minimum value of the HAA/OAA ratio in Hartnup disorder was 2.4, while the maximum value of the HAA/OAA ratio in other aminoacidurias was 1.6 (Table 2, Fig. 2A).

Computation of the HAA/OAA ratio required quantification of all included amino acids (Table 2). Acknowledging that this is not standard practice in many metabolic diagnostic laboratories, we also evaluated the performance of a ratio using a limited set of amino acids, specifically aiming to distinguish Hartnup disorder from generalized aminoaciduria. Only six amino acids were quantified in all samples of patients with generalized aminoaciduria: serine, alanine, glycine, histidine, cystine and lysine. Of these amino acids, the differences in fold changes between these two patients groups were the largest for alanine, glycine and histidine. The ratio of the fold change of alanine over the mean fold change of glycine and histidine clearly discriminated Hartnup disorder from generalized aminoaciduria, with a mean Ala/(Gly + His) ratio in the Hartnup cohort of 4.3, contrasting with a mean Ala/(Gly + His) ratio of only 0.7 in the generalized aminoaciduria cohort. Even for this limited ratio, there was no overlap between the two cohorts, as the minimum value in the Hartnup cohort was 2.7, while the maximum value for the ratio in generalized aminoaciduria was 1.3 (Table 2, Fig. 2B).

4. Discussion

In this study we demonstrated that quantitative assessment of the degree of the increases, rather than qualitative assessment of increases of amino acid excretion, enhances correct discrimination of Hartnup disorder from other aminoacidurias. We introduce the HAA/OAA ratio as a new and easily applicable diagnostic tool to discriminate Hartnup disorder from other aminoacidurias. Moreover, we demonstrate that even the limited Ala/(Gly + His) ratio, requiring quantification of only three amino acids, can distinguish Hartnup disorder from generalized aminoaciduria.

Quantification of all urinary amino acid concentrations revealed that, in addition to the amino acids reported to be excreted excessively in Hartnup disorder (Nanto-Salonen et al. 2006, Vademecum Metabolicum), cystine, alpha-aminobutyric acid, glycine, lysine, citrulline, glutamic acid, aspartic acid and arginine can be increased as well in the urine of patients with Hartnup disorder [2,3,6]. Unexpectedly, the excretion of histidine, an amino acid of which the intestinal uptake and tubular reabsorption is expected to be affected (Nanto-Salonen et al. 2006, Vademecum Metabolicum), was increased only modestly in 18/20 samples, contrasting with the extent of the excretion of HAA. Whether the complete range of amino acids excreted by patients with Hartnup disorder can be explained by a broader substrate specificity of the B^0 AT1 transporter than currently described, or whether the aberrant transport of amino acids in the proximal tubule of patients with Hartnup disorder affects (saturation of) other amino acid

Table 2
HAA/OAA ratio and Ala/(Gly + His) ratio in Hartnup disorder versus other aminoacidurias.

	Patients	Samples	FULL RATIO: HAA/OAA			LIMITED RATIO: ALA/(GLY + HIS)		
			Mean FC HAA	Mean FC OAA	HAA/OAA ratio (mean (range))	FC Alanine	Mean FC Gly and His	Ala/(Gly + His) ratio (mean (range))
Hartnup disorder – Utrecht	4	20	19.7	3.7	6.1 (3.1–9.2)	10.5	2.5	4.2 (2.7–9.8)
Hartnup disorder – Potter et al.	7	7	12.0	1.9	6.2 (2.4–9.6)	11.9	2.5	4.7 (4.0–6.2)
Hartnup disorder – Combined	**11**	**27**	**17.7**	**3.2**	**6.1 (2.4–9.6)**	**10.9**	**2.5**	**4.3 (2.7–9.8)**
Generalized aminoaciduria	7	10	7.2	6.2	1.0 (0.5–1.6)	**4.7**	**7.2**	**0.7 (0.4–1.3)**
Lysinuric protein intolerance	2	16	1.6	10.5	0.2 (0.1–0.5)	2.5	1.7	1.8 (1.0–3.5)
Cystinuria	7	42	1.2	37.0	0.0 (0.0–0.1)	0.7	1.6	0.6 (0.2–1.7)
Aminoaciduria – Combined	**16**	**68**	**2.3**	**25.7**	**0.2 (0.0–1.6)**	1.8	2.6	0.9 (0.2–3.5)

Abbreviations: Ala: alanine; FC: fold change; Gly: glycine; HAA: Hartnup amino acids; His: histidine; OAA: other amino acids.
Bold signifies P < 0.0001

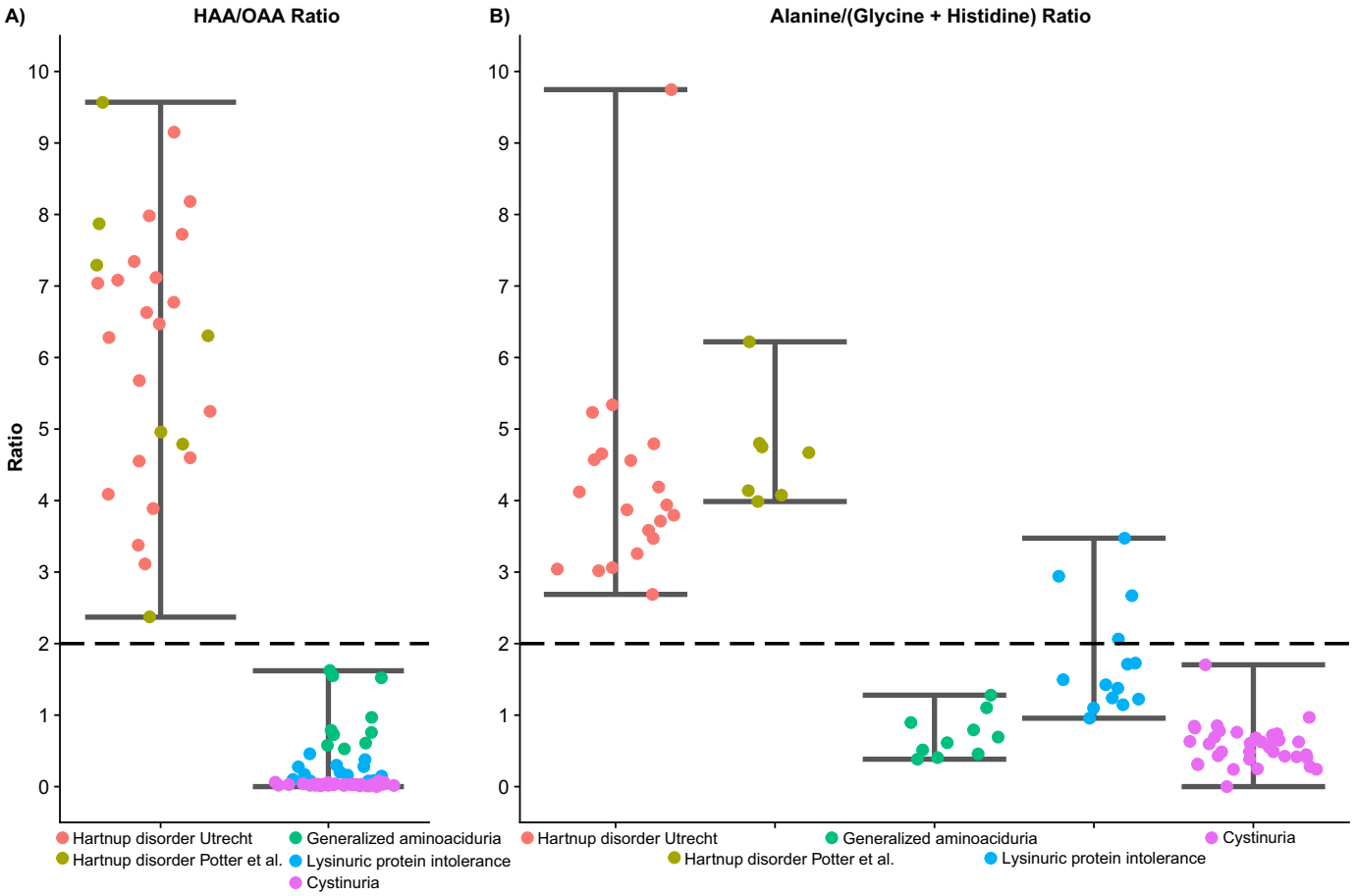

Fig. 2. HAA/OAA ratio and Ala/(Gly + His) ratio in Hartnup disorder versus other aminoacidurias.
The Hartnup disorder cohort from Utrecht is depicted in orange, the Hartnup disorder cohort of Potter et al. is depicted in brown. Generalized aminoaciduria is depicted in green, lysinuric protein intolerance is depicted in blue and cystinuria is depicted in magenta. The error bar depicts the minimum and maximum values of the presented group. A) The y-axis depicts the HAA/OAA ratio. The x-axis distinguishes patients with Hartnup disorder from patients with other aminoacidurias. The dashed line at ratio = 2 depicts the cut-off value between Hartnup disorder and other aminoacidurias. B) The y-axis depicts the Ala/(Gly + His) ratio. The x-axis distinguishes the five patient groups. The dashed line at ratio = 2 depicts the cut-off value between Hartnup disorder and generalized aminoaciduria. Abbreviations: Ala: alanine; FC: fold change; Gly: glycine; HAA: Hartnup amino acids; His: histidine; OAA: other amino acids. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

transporters remains to be elucidated.

It is of interest that the Hartnup disorder cohort derived from Potter et al. described a less generalized aminoaciduria in their patients, even though the same reference values were used. We speculate that differences in the patient age at time of sampling (all adults in Potter et al.) may affect the amino acid excretion pattern. Moreover, differences in nutrition, particularly a higher protein intake, could have contributed to the here observed more pronounced generalized aminoaciduria [3]. Still, despite these differences, the distribution of the calculated ratios is comparable, corroborating the accuracy of these ratios in discriminating Hartnup disorder from other aminoacidurias. However, given the relatively small sample sizes of the two cohorts, it would be of interest to assess the generalizability of the calculated ratio in another, independent cohort of patients with Hartnup disorder.

As nutritional intake, including protein intake, has been increasing in many countries over the past decades [3], the degree to which individuals with Hartnup disorder demonstrate amino acid excretion patterns mimicking generalized aminoaciduria might increase as well, explaining why quantification of urinary amino acid concentrations was not required in the past, but is expedient now.

In conclusion, we here report that excretion values of amino acids not classically related to Hartnup disorder, are frequently elevated in patients with Hartnup disorder. This may induce a risk of misdiagnosis as generalized aminoaciduria and preclusion from vitamin B3 treatment. By changing the focus from absolute to relative increase of amino acid excretion and by calculating the HAA/OAA ratio, we introduce a diagnostic tool that enhances correct discrimination of Hartnup disorder from other aminoacidurias.

Take home message

The fold change ratio of Hartnup amino acids over other amino acids ensures correct diagnostic differentiation of Hartnup disorder from other aminoacidurias.

Guarantor for the article

J.J.M. Jans declares that she will accept full responsibility for the work and the conduct of the study. She had access to all the data and controlled the decision to publish.

Compliance with ethics guidelines

All procedures followed were in accordance with the ethical standards of the University Medical Center Utrecht and with the Helsinki Declaration of 1975, as revised in 2000. No patient informed consent was required for this study, since all patient data was anonymized.

Details of contributions of individual authors

J.J.M.J. and P.M.v.H. conceptualized and designed the study and supervised data collection and analysis. J.J.M.J., H.C.M.T.P. and M.G.M.S.v.d.V. collected the data. H.A.H. performed the data analysis and drafted the initial manuscript. All authors critically reviewed the initial manuscript and approved the final version as submitted

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Declaration of Competing Interest

All authors state that they have no competing financial interests to declare. None of the authors accepted any reimbursements, fees or funds from any organization that may in any way gain or lose financially from the results of this review. The authors have not been employed by such an organization. The authors have not act as an expert witness on the subject of the review. The authors do not have any other competing financial interest.

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References

[1] N. Blau, M. Duran, K.M. Gibson, Laboratory Guide to the Methods in Biochemical Genetics, Springer-Verlag, Berlin-Heidelberg, 2008.
[2] S. Bröer, The role of the neutral amino acid transporter B0AT1 (SLC6A19) in Hartnup disorder and protein nutrition, IUBMB Life 61 (6) (2009) 591–599.
[3] S.M. Camargo, D. Bockenhauer, R. Kleta, Aminoacidurias: clinical and molecular aspects, Kidney Int. 73 (8) (2008) 918–925.
[4] C.K. Cheon, B.H. Lee, J.M. Ko, H.J. Kim, H.W. Yoo, Novel mutation in SLC6A19 causing late-onset seizures in Hartnup disorder, Pediatr. Neurol. 42 (5) (2010) 369–371.
[5] J.W. Foreman, Fanconi syndrome, Pediatr. Clin. N. Am. 66 (1) (2019) 159–167.
[6] K. Javed, Q. Cheng, A.J. Carroll, T.T. Truong, S. Bröer, Development of biomarkers for inhibition of SLC6A19 (B0AT1)-a potential target to treat metabolic disorders, Int. J. Mol. Sci. 19 (11) (2018).
[7] R. Kleta, E. Romeo, Z. Ristic, et al., Mutations in SLC6A19, encoding B0AT1, cause Hartnup disorder, Nat. Genet. 36 (9) (2004) 999–1002.
[8] R. Kleta, Fanconi or not Fanconi? Lowe syndrome revisited, Clin. J. Am. Soc. Nephrol. 3 (5) (2008) 1244–1245.
[9] H.L. Levy, Hartnup disorder, in: C.R. Scriver, W.S. Sly, D. Valle (Eds.), The Metabolic and Molecular Bases of Inherited Diseases, McGraw-Hill, New York, 2001.
[11] S.J. Potter, A. Lu, B. Wilcken, K. Green, J.E. Rasko, Hartnup disorder: polymorphisms identified in the neutral amino acid transporter SLC1A5, J. Inherit. Metab. Dis. 25 (6) (2002) 437–448.
[12] E. Romeo, M.H. Dave, D. Bacic, et al., Luminal kidney and intestine SLC6 amino acid transporters of B0AT-cluster and their tissue distribution in Mus musculus, Am J Phsyiol Renal Physiol 209 (2) (2006) 376–383.
[13] H.F. Seow, S. Bröer, A. Bröer, et al., Hartnup disorder is caused by mutations in the gene encoding the neutral amino acid transporter SLC6A19, Nat. Genet. 36 (9) (2004) 1003–1007.
[14] B. Wilcken, J.S. Yu, D.A. Brown, Natural history of Hartnup disease, Arch. Dis. Child. 51 (1) (1977) 38–40.
[15] P.W. Wong, A.M. Lambert, P.M. Pillai, P.M. Jones, Observations on nicotinic acid therapy in Hartnup disease, Arch. Dis. Child. 42 (226) (1967) 642–646.