Case Report

Moderate Hyperhomocysteinemia along with Increased Levels of Vitamin B₁₂ in a 21-Year-Old Male with the Sanfilippo Syndrome: A Case Report

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Keywords

Homocysteine · Vitamin B₁₂ · Sanfilippo syndrome · Cystathionine · Case report

Abstract

The Sanfilippo syndrome is an autosomal recessive mucopolysaccharidosis. Homocysteine and B₁₂ status have not been described in this syndrome. A 21-year-old bedridden male with the Sanfilippo syndrome was hospitalized. He was in poor nutritional status according to laboratory and somatometric findings, he had an enlarged liver, moderate aortic valve insufficiency and was under antiepileptic, antipsychotic and anti-cholinergic therapy. The patient had moderate hyperhomocysteinemia (16.9 μmol/L) with co-existing high levels of serum B₁₂ (1,765

pg/mL). In addition, cystathionine, methionine sulfoxide and certain amino acids were measured. It was hypothesized that a “functional” deficiency of vitamin B₁₂ may be due to problematic transcobalamin-vitamin B₁₂ complex dissociation. Moreover, the patient’s cardiovascular background and/or medical treatment may explain the observed hyperhomocysteinemia. B₁₂ and homocysteine status should be assessed in Sanfilippo patients. This report suggests that checking vitamin B₁₂ and homocysteine status may be useful in the Sanfilippo syndrome.

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Published by S. Karger AG, Basel

Introduction

The Sanfilippo syndrome is an autosomal recessive mucopolysaccharidosis caused by deficiency in an enzyme responsible for the lysosomal degradation of the glycosaminoglycan heparan sulfate [1]. As a result, heparan sulfate accumulates in various organs and tissues [1]. Although heterogeneity exists, the most common manifestations of the syndrome include developmental delay, aggressive behavior, neurological symptoms, seizures, etc. [1]. To our knowledge, there is no other report of disturbed homocysteine metabolism in the Sanfilippo syndrome.

Case Presentation

A 21-year-old bedridden male with mucopolysaccharidosis type III, also known as Sanfilippo syndrome (subtype B), was hospitalized to place a gastrostomy feeding tube due to frequent aspirations and inability to be adequately fed per os.

The patient was not able to communicate with the doctors but the co-operation with his family was satisfactory. He was under anti-epileptic, antipsychotic and anti-cholinergic treatment. From the patient’s history, it was shown that he had a respiratory infection 3 months ago treated with antibiotics. Moreover, he had increased liver size, borderline enlarged spleen, dolichocolon, and bowel wall thickening, which may imply malabsorption. From the ultrasonography, an aortic valve insufficiency was demonstrated as well as heart wall thickening. The patient was on metronidazole benzoate and ceftriaxone sodium trisesquihydrate treatment due to respiratory infection.

His body weight was 43 kg and his knee height was 51 cm, corresponding to 146 cm height based on the following equation: $64.19 - (0.04 \times \text{age}) + (2.02 \times \text{knee height})$. His body mass index was 20.1 kg/m² and his mid-arm circumference was 25 cm (<5th percentile).

According to the dietary recall for a typical weekday, the patient’s dietary intake was as follows: energy: 1,490 kcal; protein: 68 g; carbohydrate: 143 g; total fat: 72.6 g; calcium: 1,400 mg; potassium: 2,101 mg; sodium: 1,073 mg; copper: 452 mg; iron: 6.8 mg; magnesium: 188 mg; phosphorus: 1,130 mg; zinc: 6.3 mg; vitamin A: 1,269 RAE; vitamin B6: 1.4 mg; vitamin B₁₂: 4.5 µg; vitamin C: 26 mg; vitamin D: 9.6 µg; vitamin E: 9.2 mg; folate: 238 µg; thiamin: 1.1 mg; riboflavin: 2.2 mg (analysis with the Food Tracker program

<https://www.supertracker.usda.gov/foodtracker.aspx>). The patient had suboptimal intake of energy, dietary fiber, potassium, copper, iron, magnesium, zinc, vitamins C, D, E and folate. However, the week preceding hospitalization, the patient had an even more reduced food and liquid intake.

The patient's laboratory values upon admission are presented in Table 1. The patient was in poor nutritional status as evidenced by his low mid-arm circumference, low leukocyte count ($1.2 \times 10^9/L$), hematocrit (32.5%) and hemoglobin (11.0 g/dL). He also had low albumin levels which may be affected by inflammation [2].

The patient had moderate homocysteinemia (16.9 $\mu\text{mol/L}$) with co-existing high levels of serum B₁₂ (1,765 pg/mL) and normal levels of choline and betaine (shown in Table 2 and Fig. 1). He had high levels of cystathionine, which is produced from homocysteine through trans-sulfuration and high levels of methionine sulfoxide, which is a metabolite of methionine deriving from homocysteine methylation (shown in Fig. 1). Several amino acids were abnormal, i.e., glycine, serine, arginine, threonine and tryptophan.

It is to be noted that the patient has recently been contacted by phone. He is in good health and now is 26 years old. All procedures were in accordance with ethical standards of human experimentation and the mother of the patient gave informed consent for this study. The CARE guidelines for case reports were followed (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000512215).

Discussion/Conclusion

Homocysteine is synthesized from methionine via demethylation. Then, it is either remethylated to methionine or trans-sulfurated to cysteine [3]. Several nutrients are implicated in these processes such as folate, vitamin B₆, vitamin B₁₂, methionine, choline and betaine [3], most of which were measured in the present work. Increased intake of the aforementioned nutrients has been connected to lower circulating homocysteine [3]. However, in this case increased levels of vitamin B₁₂ co-existed with moderate hyperhomocysteinemia, and increased cystathionine and methionine sulfoxide.

Increased levels of B₁₂ may be documented in several pathological conditions such as liver diseases, cancer, renal insufficiency or excess intake [4]. In the present case, liver enzymes were only borderline elevated with the exception of γ -GT, renal function was normal, while no neoplasm or supplemental use of B₁₂ was reported. Thus, it was hypothesized that the patient has a “functional” deficiency of B₁₂, which may be related to increased homocysteine [4]. Briefly, vitamin B₁₂ circulates as a complex with transcobalamin, which enters the cells by endocytosis and then it is dissociated from transcobalamin in lysosomes [5]. On the grounds of a lysosomal storage disease, such as the Sanfilippo syndrome, we hypothesize that the dissociation of transcobalamin-vitamin B₁₂ may be problematic resulting in increased concentration of the transcobalamin-vitamin B₁₂ complex and “functional deficiency” with low amounts of intracellular bioavailable B₁₂. Moreover, increased levels of serine and threonine have been observed in B₁₂ deficient mice [6], a phenotype also present in this case. An increased degradation of tryptophan to kynurenine has been related to increased homocysteine levels, which

is in line with our findings [7]. Moreover, the route of betaine utilization for homocysteine remethylation [3] seems activated, since its metabolites dimethylglycine, glycine and serine are increased.

Another explanation of the observed hyperhomocysteinemia may lay in the cardiac problems of the patient (cardiac valve disease). Indeed, narrowing of coronary artery luminal and glycosaminoglycan deposition as well as cardiac valve diseases have been observed in patients with Sanfilippo syndrome [8] and homocysteine increases in atherosclerosis [3].

Another point that deserves attention is the role of heparan sulfate, which is elevated in patients with the Sanfilippo syndrome [1]. Homocysteine has been shown to down-regulate heparan sulfate synthesis in vitro [9], but it is unknown how increased heparan sulfate may affect homocysteine and related metabolites. Moreover, heparan sulfate may bind to arginine containing molecules [10], which may explain the observed increased levels of arginine. Last but not least, medical treatment may influence both homocysteine and B₁₂ levels [11].

The strength of the present work is the in-depth analysis of several metabolites implicated in homocysteine metabolism. Limitations of the present work lay on its nature; it is a case report and the observed results cannot be generalized.

In summary, we reported a case study of moderate hyperhomocysteinemia with co-existing high levels of serum B₁₂ and other micronutrient alterations. A “functional” deficiency of B₁₂ was hypothesized, while the patient’s cardiovascular background and/or medical treatment may also explain hyperhomocysteinemia. B₁₂ and homocysteine status assessment may be plausible in Sanfilippo patients. This case report serves at sensitizing clinicians in assessing vitamin B₁₂ and homocysteine status in Sanfilippo patients.

Acknowledgements

The authors would like to thank Prof. Smaragdi Antonopoulou and Ms. Agathi Ntzouvani for their help in blood transfer and analysis.

Statement of Ethics

The study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Written informed consent was obtained from the patient’s mother for publication of this case report.

Conflicts of Interest Statement

The authors have no conflicts of interest to declare.

Author Contributions

P.D. contributed to the conception of the work, the analysis of results, writing of the manuscript and final approval. M.C. contributed to the conception of the work, acquisition of the data, analysis of results and critically reviewing the manuscript. G.K. contributed to the conception of the work and the analysis of results. M.D. contributed to the analysis of results and drafting of the manuscript. V.P. contributed to the analysis of results, writing of the manuscript and final approval. M.K. contributed to the acquisition of the data, analysis of results, critically reviewing and final approval. C.K. contributed to the acquisition of the data, analysis of results, critically reviewing and final approval. M.K.L. contributed to the analysis of results, critically reviewing the manuscript and final approval.

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Fig. 1. Homocysteine and related nutrients. Homocysteine is synthesized from methionine via demethylation. Then, it is either remethylated to methionine or trans-sulfurated to cystathionine in a reaction catalyzed by cystathionine β -synthase with vitamin B₆ as a cofactor. Nutrients acting as methyl donors for homocysteine remethylation include choline, through its intermediate oxidation to betaine, and folate with B₁₂ as a cofactor. Several amino acids are also connected to homocysteine cycle, such as glycine, serine, cysteine, taurine, arginine, lysine and methionine. Hcy, homocysteine; THF, tetrahydrofolate; mTHF, methyl-tetrahydrofolate; MetSO, methionine sulfoxide; PSP, phosphoserine phosphatase.

Table 1. Selected biochemical characteristics of the subject upon admission

Parameter (units)	Value	Reference values
White blood cells ($\times 10^3/\mu\text{L}$)	2.9	5–10 ³ /μL ^a
Red blood cells ($\times 10^6/\mu\text{L}$)	3.62	4.2–5.4 for men ^a
Hematocrit (%)	32.5	36–48 for men ^a
Hemoglobin (g/dL)	11.0	12–16 for men ^a
MCV (fL)	89.9	82–98 ^a
MCH (pg)	30.3	26–34 ^a
MCHC (g/dL)	33.7	31–37 ^a
RDW (%)	13.9	11.5–14.5 ^a
Platelet count ($\times 10^3/\mu\text{L}$)	165	140–400 ^a
Mean platelet volume (fL)	6.9	7.4–10.4 ^a
Creatinine	0.4	0.7–1.5
Urea	14	6–22
Albumin (mg/dL)	3,070	3,500–5,000
K (mmol/L)	4.3	3.5–5.1
Mg (mmol/L)	2.0	1.4–2.7
Ca (mg/dL)	8.9	8.5–10.7
P (mg/dL)	3.7	2.7–4.5
Bilirubin (mg/dL)	0.44	0.2–1.0
SGOT (U/L)	43	10–34
SGPT (U/L)	45	10–44
γ-GT (U/L)	116	11–50
CPK (U/L)	83	24–104
LDH (U/L)	293	211–480
ALP (U/L)	84	45–422
Total-cholesterol (mg/dL)	106	<200
LDL-cholesterol (mg/dL)	72	<130
HDL-cholesterol (mg/dL)	24	>55
Triacylglycerols (mg/dL)	49	<150
Ferritin (ng/mL)	118	30–400 (for men)
Prothrombin time (s)	15.2	13.3 (control)
Activated partial thromboplastin time (APTT) (s)	41.9	28.0–40.0
Fibrinogen (mg/dL)	192	200–400
D-dimer (μg/mL)	2.22	<0.5

^a The reference values are those provided by Fischbach (Fischbach F.T.: A manual of laboratory and diagnostic tests. 5th ed. 1988, Philadelphia: Lipincott-Raven). All other values are provided by the hospital's biochemical department.

Table 2. Biomarkers related to homocysteine cycle and amino acids profile

Parameter (units)	Value	Reference values
Homocysteine (μmol/L)	16.9	4.72–14.05
Vitamin B ₁₂ (pg/mL)	1,765	160–950
Folate (ng/mL)	6.7	4.6–18.7
Choline (μmol/L)	10.4	5–12
Betaine(μmol/L)	24.7	16–51
Dimethylglycine (μmol/L)	5.215	1.5–4
Methionine (μmol/L)	33.25	18–33
Methionine sulfoxide(μmol/L)	1.365	<0.5
Arginine (μmol/L)	95.5	10–80
Methylmalonic acid (μmol/L)	0.13	<0.26
Alanine (μmol/L)	300	230–510
Glycine (μmol/L)	686	200–300
Valine (μmol/L)	189	150–350
Leucine (μmol/L)	105	70–170
Isoleucine (μmol/L)	58	40–140
Threonine (μmol/L)	280	70–240
Asymmetric dimethyl arginine (μmol/L)	0.778	0.5–0.8
Homoarginine (μmol/L)	0.5855	1.2–3.3
Trimethyl lysine (μmol/L)	0.7205	0.4–1.3
Total cysteine (μmol/L)	298	150–350
Cystathionine (μmol/L)	0.95	<0.4
Trimethyl amine oxide (TMAO)(μmol/L)	0.00327	3.5 (2.4–5.9) ^a
Proline (μmol/L)	179	110–360
Asparagine (μmol/L)	15.7	20–130
Serine (μmol/L)	298	95–125
Glutamine (μmol/L)	523	390–700
Glutamic acid (μmol/L)	51	20–140
Phenylalanine (μmol/L)	79	26–85
Ornithine (μmol/L)	90	30–90
Lysine (μmol/L)	134	120–290
Histidine (μmol/L)	108	70–140 ^b
Tyrosine (μmol/L)	44	40–110
Tryptophan (μmol/L)	35	43–89
Kynurenine (μmol/L)	0.6	1.6–2.9

The reference values are those provided by Bevitall AS, Bergen, Norway, unless otherwise reported.

^a Median (25th–75th) for adults free of cardiovascular disease based on: Tang WH, et al.: N Engl J Med. 2013;368:1575–84. ^b Reference value based on Lord et al. 2008, Canada: Metamatrix Institute.