A mild case of sodium-dependent multivitamin transporter (SMVT) deficiency illustrating the importance of treatment response in variant classification

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Abstract Sodium-dependent multivitamin transporter (SMVT) deficiency is a recently described multivitamin-responsive inherited metabolic disorder (IMD) of which the phenotypic spectrum and response to treatment remains to be elucidated. So far, four pediatric patients have been described in three case reports with symptoms ranging from severe neurodevelopmental delay to feeding problems and failure to thrive, who demonstrated significant improvement after initiation of enhancement of targeted multivitamin treatment (biotin, pantothenic acid, and lipoic acid). We describe a fifth case of a patient presenting at the relatively mild end of the phenotypic spectrum with failure to thrive, frequent vomiting and metabolic acidosis with hypoglycemia, and mild osteopenia, who was diagnosed with SMVT deficiency due to compound heterozygous variants in SLC5A6. Additional genetic testing of variants of unknown significance (VUSs) as well as the clinical improvement in all aspects of the patient’s disease upon initiation of treatment with biotin and pantothenic acid (plus lipoate as antioxidant) aided in the confirmation of this diagnosis. This case report aims to enhance recognition of the broad phenotypic spectrum of SMVT deficiency due to SLC5A6 mutations and discusses the different treatment strategies. It demonstrates how combining biochemical and genetic testing with the evaluation of (early) treatment response (i.e., using a “diagnostic therapeuticum”) can influence confirmation of pathogenicity of genomic variants.

[Supplemental material is available for this article.]

INTRODUCTION

Multivitamin-Responsive IMDs
Inherited metabolic disorders (IMDs) comprise a continuously expanding class of rare genetic disorders, of which more than 1500 have been identified since the first IMD alkaptonuria was proposed in 1902 by Sir Archibald Garrod (Garrod 1902; www.iembase.org). Because of
the rapidly progressing developments in the field of genetics, with expanding knowledge of the underlying pathophysiology caused by the impairment in the metabolic pathway(s) involved, Ferreira et al. (2019, 2021) proposed an up-to-date nosology (International Classification of Inherited Metabolic Disorders [ICIMD]; www.icimd.org), consisting of a hierarchical, group-based classification of all currently known IMDs. Within this classification, the disorders of vitamin and cofactor metabolism account for 73 IMDs, encompassing a relatively large, potentially treatable group of IMDs because vitamin supplementation is usually readily available and safe and has been proven to be very efficient, especially if given early on in the disease course (Ferreira et al. 2019, 2021; Mandia et al. 2021). Therefore, timely recognition and knowledge of treatment strategies is paramount. Reviewing the treatment strategies of these 73 IMDs shows that, thus far, only a few of those IMDs are known to be multivitamin-responsive—that is, treatable by supplementation of two or more vitamins. One example of such an IMD is biotin-thiamine-responsive basal ganglia disease (BTBGD), which is characterized by (subacute) encephalopathy, seizures and other neurological symptoms, presenting in childhood, early infancy, or adulthood (Tabarki et al. 2013; Ortigoza-Escobar et al. 2014).

Biotin and thiamine are given as early in the disease course as possible and are continued lifelong. Here, we present an illustrative case vignette of another such treatable multivitamin-responsive IMD: the recently reported sodium-dependent multivitamin transporter (SMVT) deficiency. The phenotype, genotype, and treatment response of our patient are compared to other cases described in literature. By sharing knowledge and the diagnostic process of single cases affected by this rare disease and comparing treatment strategies, we aim to pave the way for future recognition and treatment of SMVT-deficient patients. Moreover, it demonstrates the importance of phenotype enhanced genotyping.

What Do We Know about SMVT Deficiency Currently?

Among the disorders of vitamin metabolism, SMVT deficiency is a recently described inherited metabolic disorder with so far a broad phenotypic spectrum ranging from feeding problems, failure to thrive, metabolic acidosis, and mild to severe neurological deficits. Responses to treatment differ between cases. SMVT is encoded by SLC5A6 located on Chromosome 2p23.3. This transmembrane protein transports the water-soluble vitamins pantothenic acid (vitamin B5) and biotin (vitamin B7) and the metabolite lipoate in the presence of sodium in both the digestive system and across the blood–brain barrier (Balamurugan et al. 2003; Sabui et al. 2018). Having recessive variants in SLC5A6 causing SMVT deficiency is a recently described inherited metabolic disorder. Clinically, the disease mimics biotinidase deficiency with a broad phenotypic spectrum ranging from feeding problems, failure to thrive, metabolic acidosis, and mild to severe neurological deficits (Schwantje et al. 2019).

Biotin is an essential micronutrient, vital in normal cellular metabolism, growth, and development, as well as acting as an essential cofactor in the different carboxylase enzymes known to be active in various metabolic pathways, including gluconeogenesis (pyruvate carboxylase), catabolism of amino acids (propionyl-CoA carboxylase and 3-methylcrotonyl-CoA carboxylase), and fatty acid synthesis (acetyl-CoA carboxylase) (McMahon 2002; Said 2012). In addition, biotin plays a role in energy metabolism, cellular oxidative stress regulation, and gene expression, as well as enabling normal immune functioning (Rodriguez-Melendez and Zempleni 2003; Madsen et al. 2015). Deficiency of biotin can lead to a variety of clinical symptoms including failure to thrive, neurological disorders such as ataxia, developmental delay and seizures, and impairment in bone development, as well as dermatological features (Mock et al. 1981; Wolf 2012; Ghosal et al. 2013).

Pantothenic acid is also an essential micronutrient, functioning as a precursor of coenzyme A, which in turn plays an indispensable role in fatty acid oxidation, and to a lesser extent
in carbohydrate and protein metabolism (Lederer et al. 1971; Said 2011). Pantothenic acid deficiency leads to disturbed intermediary metabolism; that is, it impairs CoA biosynthesis, stimulates polyol-pathway activity, impairs glycolysis and tricarboxylic acid cycle activity, and modifies urea metabolism, as evident on organic acid, amino acid, and acylcarnitine profiles. Lipoate is one of the cofactors in the glycine cleavage system and the pyruvate dehydrogenase, branched chain ketoacid dehydrogenase, and ketoglutarate dehydrogenase complexes. It catalyzes redox reactions in the mitochondrial energy production, enabling oxidative decarboxylation reactions of amino acids and keto acids, as well as providing antioxidative, and anti-inflammatory effects (Morikawa et al. 2001). Lipoate deficiency is associated with encephalopathy and other neurological disorders as well as low bone density (Mayr et al. 2011; Roberts and Moreau 2015).

Ghosal et al. (2013) found that mice with intestine-specific deletion of SMVT either died prematurely or displayed significant growth retardation, decreased bone density and length, and lethargic behavior compared to controls. Sabui et al. (2018) showed that intestinal-specific SMVT knockout of the mouse was associated with growth retardation. They also developed spontaneous and severe inflammation causing early death. All clinical features were completely reversed by biotin and pantothenic acid supplementation.

**CASE VIGNETTE OF SMVT DEFICIENCY**

**Case Report**

Our case is a currently 5-yr-old girl. She was born as the first child to healthy, nonconsanguineous parents after an uncomplicated term pregnancy. She was noted as small for gestational age (SGA) at 2650 grams (<P5), but further physical examination revealed no dysmorphic features or microcephalia. Soon after birth, feeding difficulties became apparent with frequent vomiting and failure to thrive. Antacid treatment was started for suspected gastroesophageal reflux disease, with temporary positive effect. Her psychomotor development was age-appropriate, albeit she was described as somewhat clumsy. She was easily fatigued apparently because of a lack of energy and had very dry, eczematous skin. Laboratory findings showed mild osteopenia for which supplements of vitamin D and calcium were started. She was frequently hospitalized the first 2 years of her life because of persistent vomiting, diarrhea, and insufficient oral intake resulting in dehydration and ketotic hypoglycemia requiring nasogastric (NG) or intravenous rehydration. From the age of 1.5 to 2 yr old, she was fed through an NG and nasoduodenal (ND) tube. At 2 yr of age she was admitted to the pediatric intensive care unit (PICU) with severe metabolic decompensation (pH 7.10, lactate 3 mmol/L, glucose 1.7 mmol/L, ketones 6 mmol/L) in the course of a gastrointestinal viral infection. She recovered from this episode but suffered from subsequent periods of cyclic vomiting with a tendency to ketoacidosis. Extensive additional testing was done, with high suspicion of an underlying metabolic disorder.

**Diagnostic Confirmation and Treatment**

Metabolic screening performed in plasma and urine showed nonspecific subtle elevations of various organic acids including 3-hydroxyisovaleric acid, lactic acid, and 3-hydroxybutyrate. Elevated lactate levels as observed in plasma and urine of the patient points to the impaired degradation of pyruvate and is a characteristic finding in patients with biotinidase deficiency as well as in patients with a defect in the biosynthesis of lipoic acid and, in fact, patients with a defect in the biosynthesis of coenzyme A as in PKAN2 deficiency. Furthermore, 3-hydroxyisovaleric acid is one of these typical metabolites that is elevated in biotinidase deficiency. Chromosomal microarray did not reveal pathogenic copy-number variants. Trio-based
whole-exome sequencing (trio-WES) was performed in the EN-ISO 15189:2012 certified clinical DNA diagnostics laboratory Amsterdam UMC Genome Diagnostics (AGDx). This revealed compound heterozygous potential pathogenic variants in **SLC5A6** (NM_021095.4): c.1005 + 1G > A, predicted to affect splicing, and c.1865_1866del, introducing a shift of the reading frame (p.(Gln622Argfs∗51)) (Table 1). Subsequent **SLC5A6** cDNA analysis, performed on reverse transcription (RT)-transcribed mRNA isolated from cultured primary skin fibroblasts of the patient, confirmed the incorrect splicing of intron 9 because of the c.1005 + 1G > A variant resulting in retention of 61 bp of intron 9 and predicted to result in a nonfunctional protein (p.(Phe336Serfs∗57)). In addition, the mis-spliced allele was less abundant, which may be because of nonsense-mediated mRNA decay (see Supplemental Fig. S1). This variant was reported 1/152142 in gnomAD v3.1.2 (https://gnomad.broadinstitute.org/) and 1/996 in the Genome of the Netherlands (GoNL) database (https://www.nlgenome.nl/). Based on these findings we classify the variant as pathogenic (PVS1, PS3_Supporting, PM3_Supporting, PM2_Supporting, PP4) (Richards et al. 2015). The c.1865_1866del variant results in a shift of reading frame as a consequence of which the carboxy-terminal 13 amino acids will be substituted by 50 other amino acids (p.(Gln622Argfs∗51)).

The carboxyl terminus of SMVT is not well-conserved among species so the consequences of this variant for protein functioning remain unclear. Because it was previously reported in another patient with SMVT deficiency (Schwantje et al. 2019), we considered this variant likely pathogenic (PM3, PM4, PM2_Supporting, PP4) (Richards et al. 2015). Its frequency was reported 15/152128 in gnomAD v3.1.2.

Comparison to Other Described SMVT Deficiency Cases
To the best of our knowledge, only three other case reports have appeared in which SMVT deficiency was reported due to pathogenic **SLC5A6** variants (see Table 2 for a detailed comparison). Subramanian et al. (2017) describe a severely affected patient with significant developmental delay, failure to thrive, severe gastroesophageal reflux, variable immunodeficiency, and osteoporosis. After oral supplementation was started and eventually optimized, the infant improved in growth and verbal and motor development and his immune status normalized.

Schwantje et al. (2019) presented a case of a then 3-yr-old girl with a delay in gross motor development, frequent vomiting, chronic diarrhea, and failure to thrive in the first years of
| Clinical features                  | Subramanian et al. 2017 | Schwantje et al. 2019 | Byrne et al. 2019 I-1 | Byrne et al. 2019 I-2 | This study |
|-----------------------------------|-------------------------|-----------------------|-----------------------|-----------------------|------------|
| **Neurological**                  |                         |                       |                       |                       |            |
| Neurocognitive regression         | Yes, onset infantile    | No                    | Yes, onset 14 months  | Yes, onset 12 months  | No         |
| Microcephaly                      | Yes                     | No                    | Yes, relative         | Yes, relative         | No         |
| Spasticity                        | Yes                     | No                    | No                    | No                    | No         |
| Gross motor development           | Profound delay          | Delayed               | Profound delay        | Profound delay        | Normal, but clumsy |
| Seizures                          | NR                      | No                    | No                    | Yes                   | No         |
| Peripheral neuropathy             | NR                      | No                    | NR                    | Yes                   | No         |
| Neuroimaging (MRI)                | Cerebral atrophy,      | No abnormalities      | No cerebral atrophy,  | Cerebral atrophy      | Not done   |
|                                   | brainstem (pontine),    |                       | right cerebellar      | (progressive),        |            |
|                                   | atrophy, thin corpus    |                       | hemorrhagic foci, T2/FLAIR signal hyperintensity | cerebellar atrophy (progressive), |            |
|                                   | callosum                |                       | (periventricular and parieto-occipital white matter) | brainstem (pontine) atrophy, thin corpus callosum, |            |
| Electroencephalogram (EEG)        | Normal                  | Not done              | Not done              | Background slowing (encephalopathy), epileptiform activity: generalized and multifocal spike wave (2–3 Hz) | Not done   |
| Histopathology                    | Skeletal muscle biopsy: | NR                    | Central nervous system: axonal spheroids; peripheral nervous system: undefined thickening; skeletal muscle biopsy: denervation atrophy | Cutaneous biopsy: membranous cytoplasmic inclusions | Not done   |
| Gastrointestinal                  |                         |                       |                       |                       |            |
| Feeding difficulties/ failure to  | Yes                     | Yes                   | Yes, bulbar dysfunction | Yes, bulbar dysfunction | Yes         |
| thrive                            |                         |                       |                       |                       |            |
| Nasogastric tube/ gastrostomy     | Yes                     | Yes                   | Yes                   | Yes                   | Yes        |
| feeding                           |                         |                       |                       |                       |            |
| GI hemorrhage                     | Yes                     | Yes                   | Yes                   | Yes                   | No         |

(Continued on next page.)
life, accompanied by a delay in gross motor development. Oral treatment resulted in somatic growth normalization and resolution of diarrhea. However, so far her delay in motor development persisted.

Byrne et al. (2019) described two siblings with a profound neurodevelopmental delay during infancy, with progressive ataxia, dyskinesia, and epilepsy. Severe reflux and failure to thrive were also present. At 2 yr of age, one of the siblings died of acute gastrointestinal hemorrhage following perforation of a duodenal ulcer. After initiating treatment of the second sibling, both neurological and gastrointestinal symptoms improved.

**DISCUSSION AND FUTURE DIRECTIONS**

**Diagnostic Difficulties and Treatment Strategies**

Confirmation of diagnosis in our case was established through a combination of strategies. RNA analysis was performed showing aberrant splicing of one of the SLC5A6 variants. Initiation of therapy by targeted supplementation of biotin, pantothenic acid and lipoic acid led to significant improvement of growth, development, and overall condition, comparable to the other described cases. Although several enzymes require covalently bound

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Table 2. (Continued)

| Clinical features | Subramanian et al. 2017 | Schwantje et al. 2019 | Byrne et al. 2019 I-1 | Byrne et al. 2019 I-2 | This study |
|------------------|-------------------------|-----------------------|-----------------------|-----------------------|-----------|
| Other            | NR                      | GORD                  | GORD                  | Cyclical vomiting, GORD | Cyclical vomiting, GORD |
| Hypogammaglobulinemia | Yes, IgG/IgA deficiency | NR                    | NR                    | Yes, isolated IgG deficiency | No |
| Osteopenia       | Yes                     | No                    | No                    | Yes                   | SGA      |
| Birthweight      | Normal                  | Normal                | Normal                | Normal                | SGA      |
| Metabolic acidosis with hypoglycemia | No                | Yes                   | No                    | Yes                   | Yes      |
| Easily fatigued  | NR                      | NR                    | NR                    | NR                    | Yes      |
| Dry eczematous skin | NR                   | NR                    | NR                    | Yes                   | Yes      |
| Genetic mutation SLC5A6 | c.280C>T, p.(Arg94Ter) and c.368 G>T, p.(Arg123Leu) | c.422_423del, p.(Val141fs) and c.1865_1866del, p.(Gln622Argfs*51) | c.422_423del, p.(Val141fs) and c.1199G>C, p.(R400T) | c.422_423del, p.(Val141fs) and c.1199G>C, p.(R400T) | c.1005+1G>A, p.(?) and c.1865_1866del, p.(Gln622Argfs*51) |
| Treatment        | Biotin (oral) 10–30 mg/day, pantothenic acid (oral) 250–500 mg/day, a-lipoic acid (oral) 150–300 mg/day | Biotin (oral) 10 mg twice a day, pantothenic acid (oral) 250 mg once a day | No (deceased) | Biotin (i.m.) 10 mg weekly, dexpanthenol (i.m.) 250 mg weekly, a-lipoic acid (i.v.) 300 mg weekly | Biotin (oral) 15 mg once a day, pantothenic acid (oral) 300 mg once a day, lipoic acid (oral) 300 mg once a day |

(MRI) Magnetic resonance imaging, (GI) gastrointestinal, (GORD) gastroesophageal reflux disease, (NR) not reported, (SGA) small for gestational age.
lipoamide, free lipoate is not capable of participating in this modification, at least in mammals. Indeed, the phenotype of the SVMT-deficient c-KO mouse is rescued by pantothenate and biotin without lipoate (Sabui et al. 2018). Oral administration of these supplements is well-tolerated and safe, and certainly less invasive; parenteral administration is indicated in case of vomiting, encephalopathy, and/or possible metabolic decompensation.

Our patient also had no further metabolic decompensations. In case of patients with a suspected inherited metabolic disorder but with only variants of unknown significance and/or likely pathogenic variants, in addition to performing further additional genetic testing, treating physicians could think about starting treatment in case potential benefits of treatment might outweigh the possible side effects of treatment. In case treatment diminishes clinical symptoms, preferably in different, but similar affected, not-related patients, we suggest this might be added to the classification of the identified genetic variants, in accordance with the paper by Shen et al. (2020). Importantly, such early initiation of treatment can prevent further, irreversible, organ damage.

Comparison to Other Described SMVT Deficiency Cases

When comparing all five cases, all of the patients suffered from feeding difficulties, frequent vomiting, and failure to thrive. The patients of Subramanian et al. and Byrne et al. were severely impaired neurologically, whereas our patient and that of Schwantje et al. (2019) were only described as being somewhat clumsy or with mild delays in gross motor development. This milder presentation may be related to the associated genetic variants (Byrne et al. 2019). The c.1865_1866del (p.(Gln622Argfs*51)) variant, shared by both patients, is predicted to only affect the extreme carboxyl terminus of the encoded protein and thus likely results in a protein with residual catalytic activity. Unfortunately, the activity of the protein cannot be easily assessed to confirm this. All patients except one, the first and deceased sibling described by Byrne et al., have received treatment since diagnosis. Dosages were based on the initial case description by Subramanian et al. with some variation. Subramanian et al. suggest that in case of impaired intestinal absorption or cellular uptake of biotin and pantothenic acid (and lipoic acid), as in SMVT deficiency, uptake of these nutrients by different cells at high supraphysiologic concentrations occurs via simple diffusion, thereby (at least partially) ameliorating the SMVT system. It is notable that the reported cases that were mild in nature—that is, the patient reported by Schwantje et al. (2019) and the current patient—experienced metabolic decompensations, whereas the (other) more severe cases did not. There are several possible explanations including variability in environmental triggers and severe intercurrent illness, as well as a difference in available clinical history data—that is, decompensations may have been missed.

METHODS

Medical and laboratory records were searched for data collection and extraction. DNA extraction and RNA analysis were performed according to the methods described by Maxit et al. (2017).

ADDITIONAL INFORMATION

Data Deposition and Access

Patient consent to deposit raw resequencing data was not granted. Data on the variants and phenotype are deposited in ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) and can be found under accession numbers SCV002097395 and SCV002097396.
Ethics Statement

Parents of the patient have provided written consent for publication of this case report. The Medical Ethics Board at Amsterdam UMC does not require separate study approval for the publication of single case studies.

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Author Contributions

I.H. collected clinical and genetic data, wrote the first draft, and revised and finalized the manuscript. S.N.v.d.C contributed to patient phenotyping and diagnosis and supervised data collection and drafting of the manuscript. H.R.W. performed the genetic variant interpretation and RNA studies and contributed to drafting and revision of the manuscript. R.J.A.W. performed the biochemical and metabolic data interpretation and contributed to drafting and revision of the manuscript. C.D.M.v.K. designed the study, supervised patient diagnostics, treatment, and follow-up, and supervised data collection and drafting and revision of the manuscript.

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