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CLINICAL REPORT

A new case of sodium-dependent multivitamin transporter defect occurring as a life-threatening condition responsive to early vitamin supplementation and literature review

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Abstract

Background: Biallelic pathogenic variants in *SLC5A6* resulting in sodium-dependent multivitamin transporter (SMVT) defect have recently been described as a vitamin-responsive inborn error of metabolism mimicking biotinidase deficiency. To our knowledge, only 16 patients have been reported so far with various clinical phenotypes such as neuropathy and other neurologic impairments, gastro-intestinal dysfunction and failure to thrive, osteopenia, immunodeficiency, metabolic acidosis, hypoglycemia, and recently severe cardiac symptoms.

Methods: We describe a case report of a 5-month-old girl presenting two recurrent episodes of metabolic decompensation and massive cardiac failure in the course of an infectious disease. We compare clinical, biological, and genetic findings of this patient to previous literature collected from Pubmed database (keywords: Sodium-dependent multivitamin transporter (SMVT), SMVT defect/disorder/deficiency, *SLC5A6* gene/mutation).

Results: We highlight the life-threatening presentation of this disease, the stagnation of psychomotor development, the severe and persistent hypogammaglobulinemia, and additionally, the successful clinical response on early vitamin supplementation (biotin 15 mg a day and pantothenic acid 100 mg a day). Metabolic assessment showed a persistent increase of urinary 3-hydroxyisovaleric acid (3-HIA) as previously reported in this disease in literature.

Conclusion: SMVT deficiency is a vitamin-responsive inborn error of metabolism that can lead to a wide range of symptoms. Increased and isolated excretion of urinary 3-hydroxyisovaleric acid may suggest, in the absence of markedly reduced biotinidase activity, a SMVT deficiency. Prompt supplementation with high doses of biotin and pantothenic acid should be initiated while awaiting results of *SLC5A6* sequencing as this condition may be life-threatening.

F.-X. Van Vyve and N. Mercier working as co-first authors.

KEYWORDS
biotin, cardiac failure, immunodeficiency, pantothenic acid deficiency, *SLC5A6*, SMVT

1 | INTRODUCTION

Sodium-dependent multivitamin transporter (SMVT) defect (OMIM 618973) is a recently described vitamin-responsive inborn error of metabolism mimicking biotinidase deficiency (Subramanian et al., 2017).

SMVT is a transmembrane protein expressed in multiple tissues including kidney, liver, heart, brain, and placenta. It plays a key role in water-soluble vitamins biotin and pantothenic acid and α-lipoic acid digestive absorption and regulates their cellular uptake and transport across the blood–brain barrier (Quick & Shi, 2015; Uchida et al., 2015). Biotin is a known cofactor of five carboxylases involved in various metabolic reactions including fatty acid synthesis, gluconeogenesis, and amino acid catabolism. Pantothenic acid is a Coenzyme A precursor, which is an important cofactor involved in several metabolic pathways like glycolysis and Krebs cycle. α-Lipoic acid is a cofactor covalently attached to several important mitochondrial enzymes of the intermediary metabolism and has antioxidative and anti-inflammatory effects (Quick & Shi, 2015; Said, 2011).

SMVT is encoded by *SLC5A6* gene (OMIM 604024) located on chromosome 2p23.3 (Quick & Shi, 2015). Biallelic pathogenic variants lead to a dysfunctional transporter and may therefore result in an intracellular lack of biotin, pantothenic acid, and α-lipoic acid. SMVT intestinal-knockout mice have been described with a wide spectrum of symptoms, from premature death to growth retardation and decreased bone density (Ghosal et al., 2013). Treating these mice with biotin and pantothenic acid supplementation prevented the development of intestinal mucosal abnormalities and growth retardation (Sabui et al., 2018).

To our knowledge, only 16 patients with *SLC5A6* biallelic mutations have been reported so far with various clinical phenotypes such as neuropathy and other neurologic impairments (neurodevelopmental delay, microcephaly, and brain anomalies including cerebral, brainstem, and/or cerebellar atrophy and thin corpus callosum), gastrointestinal dysfunction and failure to thrive, osteopenia, immunodeficiency, and metabolic acidosis with hypoglycemia. Cardiac involvement has been described in only five patients. Age at diagnosis of SMVT defect ranged from 19 months to 20 years of life (four postmortem) with a delay from first symptoms to diagnosis reported between 6 months and 18 years. Patients received high doses of vitamins supplementation mostly with biotin and pantothenic acid (bi-vitamin therapy) leading to improvement of their condition (Byrne et al., 2019; Hauth et al., 2022; Holling et al., 2022; Montomoli et al., 2023; Rupasinghe & Onyeador, 2023; Schwantje et al., 2019; Subramanian et al., 2017).

2 | CASE REPORT

The patient was born at 38 weeks of gestation with normal parameters. From the age of 4 months, she developed progressive failure to thrive (weight −3.5 SD, height −3.8 SD) and microcephaly (−4.5 SD) but maintained a normal psychomotor development. Family history was marked by consanguinity and the death of an older brother at the age of 8 months from unexplained multisystemic decompensation and cardiac dysfunction following a flu infection.

The patient was admitted in hospital due to a refusal to eat at the age of 5 months in a context of neurologic distress, hemodynamic shock, and ketoacidosis with normoglycemia. Venous blood gazes showed pH 7.33 (normal range: 7.37–7.45), base excess −5 mmol/L (normal range: −3.0–3.0 mmol/L), and lactate 6 mmol/L (normal range: 0–2.2 mmol/L). She was quickly admitted in pediatric intensive care unit (PICU) for invasive ventilation, inotropic support, and intravenous saline and glucose infusion. Cardiac insufficiency was rapidly identified with a left ventricular ejection fraction (LVEF) down to 32% (normal >60%). After 10 days of hospitalization, the patient was discharged with complete normalization of cardiac function (LVEF 62%) without further treatment.

Two weeks later, the patient relapsed with a further refusal to eat and vomiting. She was promptly admitted to the PICU with severe metabolic acidosis (pH 7.1, base excess −16.1 mmol/L), hyperlactatemia up to 8.8 mmol/L and a severe hemodynamic shock associated to a massive cardiac dysfunction (LVEF 17%, increased troponin up to 308 pg/mL and NT-pro-BNP up to 69,812 pg/mL). Metabolic evolution was quickly favorable with normalization of lactic acidosis after intravenous saline and glucose (up to 10 mg/kg/min) infusion, L-carnitine (100 mg/kg/d), and a daily multivitamin cocktail (B1 100, B2 50, biotin 10, and B12 1 mg) supplementation. Later, the patient underwent persistent severe refractory cardiac dysfunction despite treatment with beta-blockers, diuretics, angiotensin-converting enzyme inhibitors, and digoxin. Due to feeding problems, cyclic vomiting, and chronic diarrhea, there was poor weight gain, thus transient nasogastric tube feeding was required.

Lactic acidosis with ketonuria and an abnormal plasma acylcarnitines profile (low free carnitine, propionylcarnitine increase, normal C5OH-carnitine value, and moderate increase of long-chain acylcarnitine) were noticed during both metabolic decompensations. Remarkably, analysis of organic acids in urine revealed a persistent increase in 3-hydroxyisovaleric acid (3-HIA, between 242 and 955 mmol/mol creatinine; normal <130). Elevated level of this specific acid is associated with at least a dozen inborn errors of metabolism including biotinidase deficiency or SMVT defect; therefore, we increased the biotin supplementation to 15 mg per day nevertheless biotinidase activity was normal. Other metabolic assessments were normal including glycemia, blood ammonium, plasma amino acids, very long-chain fatty acids, urinary purine and pyrimidine, and cerebral amino acids. Fluxomic explorations of mitochondrial beta-oxidation on intact whole blood cells were non-contributive.

Severe hypogammaglobulinemia (IgG as low as 0.77 g/L [normal value: 2.08–3.87 g/L], IgM <0.05 g/L [normal value: 0.35–1.0 g/L] and IgA <0.06 g/L [normal value: 0.26–0.82 g/L]) but normal lymphocytic typing, thrombocytopenia, transient hypocalcemia, and hypophosphatemia were also observed. A viral infection was suggested as trigger for the first metabolic decompensation and a proven acute covid-19 infection for the second one. An isolated thin corpus callosum was described on a brain MRI while the brain CT scan, electroencephalogram, and lumbar puncture were normal.

Considering those two life-threatening events and an abnormally high excretion of 3-HIA in urine, whole-exome sequencing (WES) in trio was promptly performed on the parents and child. It revealed, 2 months after the first episode, a likely pathogenic, homozygous missense variant in the exon 13/17 of *SLC5A6* gene (NM_021095.4): c.1310C>T p. (Pro437Leu), inherited from each unaffected heterozygous parent. This missense substitution, confirmed by Sanger sequencing, is only recorded once in the databases of the control population (gnomAD v.3.1) and concerns an amino acid highly conserved during evolution and located in a "sodium/solute symporter" protein domain. Most of the prediction softwares evaluate this variation as potentially pathogenic (CADD score: 27.2; REVEL: pathogenic moderate 0.881; M-CAP: pathogenic supporting 0.3411).

As we were confident of the pathogenicity of the missense variant related to clinical and biochemical concordance, we added pantothenic acid 100 mg per day while waiting for availability of α-lipoic acid on the market as their efficiency has already been described in SMVT-related literature. Treatment with α-lipoic acid was then tried but had to be stopped because of oral intolerance (bitter taste leading to vomiting). The patient also received repeated immunoglobulins infusions.

Under biotin and pantothenic acid supplementation, we observed a noteworthy improvement in neurodevelopment, gradual enteral refeeding, and an impressive recovery of cardiac function with complete normalization at 3-month follow-up, allowing discontinuation of all cardiac treatments. Hypogammaglobulinemia G, M, and A quickly improved and we stopped immunoglobulins infusion at 6-month follow-up. Metabolic assessments, thrombocytopenia, and phospho-calcic balance normalized. At the last follow-up (9-month follow-up) the patient showed a normalized neurodevelopment according to her age, the absence of gastro-intestinal symptoms, a normal cardiac function, and a resolution of hypogammaglobulinemia and abnormal metabolic biochemical tests. In light of these positive responses to treatment, we can consider this variant to be likely pathogenic.

3 | COMPARISON TO OTHER CASES

Recent studies about SMVT deficiency described a specific systemic phenotype of neurological impairments (neurodevelopmental delay, microcephaly, brain anomalies, and optic nerves atrophy), gastro-intestinal dysfunction and failure to thrive, osteopenia, immunodeficiency, cardiac involvement, and metabolic acidosis (Byrne et al., 2019; Hauth et al., 2022; Montomoli et al., 2023; Rupasinghe & Onyeador, 2023; Schwantje et al., 2019; Subramanian et al., 2017). Holling et al. (2022) described furthermore five patients from three families with pleomorphic motor neuropathies with axonal and demyelinating features, without any systemic symptoms. Those patients were older (from 6 to 14 years) than those described earlier with SMVT deficiency. Vitamin supplementations led to motor improvement. Interestingly, Hsieh et al. (2022) also reported a 7-year-old female patient presenting a humoral immunodeficiency associated with compound heterozygous *SLC5A6* mutations.

Table 1 summarizes their histories, clinical phenotypes, and results of known paraclinical examinations. Table S1 (in Supplemental Information) focuses on received treatments and their effects. Table S2 (in Supplemental Information) describes extended patient's clinical data.

4 | DISCUSSION

Few authors have explained their metabolic assessments in the previous literature focusing on SMVT defect. Schwantje et al. (2019) described a patient who

TABLE 1 Compared clinical features.

Clinical features	Systemic phenotype (nine patients)	Motor neuropathies phenotype (five patients)[a]	Our study (one patient)
Demographic			
Age at onset	<6 months—14 months	6 years 9 months—13 years 6 months	5 months
Age at diagnosis	19 months—20 years (NR 2)	6 years 9 months—14 years	7 months
Sex	Female 5/9 Male 4/9	Female 4/5 Male 1/5	Female
Consanguinity	1/8 (NR 1)	0/5	Yes
Normal pregnancy	6/6 (NR 3)	NR	Yes
Small for gestational age	1/7 (NR 2)	0/5	No
Prematurity	1/7 (NR 2)	0/5	No
Trigger	Infection 3/5 Fever 2/5 (NR 4)	NR	Infection
Death	3/9	0/5	No
Neurologic			
Microcephaly	3/7 (NR 2)	0/3 (NR 2)	Yes
Developmental delay	8/9	0/5	Yes
Neurocognitive regression	3/5 (NR 4)	0/5	No
Peripheral motor neuropathy	2/3 (NR 6)	5/5	No
Hyperreflexia	2/3 (NR 6)	2/5	No
Seizure	2/7 (NR 2)	0/5	No
Other neurologic symptoms	6/8 (NR 1)	1/5	No
Abnormal brain MRI	6/8 (NR 1)	0/5	Yes
Abnormal EEG	1/3 (NR 6)	NR	No
Gastro-intestinal			
Feeding problems	6/6 (NR 3)	NR	Yes
Nasogastric tube/gastrostomy	6/6 (NR 3)	NR	Yes
Digestive troubles	Cyclic vomiting 5/7 Diarrhea 6/7 (NR 2)	NR	Cyclic vomiting Diarrhea
Gastro-esophageal reflux	7/9	NR	Yes
Gastro-intestinal hemorrhage	4/6 (NR 3)	NR	No
Failure to thrive	7/7 (NR 2)	3/5	Yes
Associated symptoms			
Low immunoglobulin levels[b]	3/8 (NR 1)	NR	Yes
Thrombocytopenia	2/2 (NR 7)	NR	Yes
Hypocalcemia and hypophosphatemia	2/2 (NR 7)	NR	Yes
Osteopenia	2/5 (NR 4)	NR	No
Metabolic acidosis	4/6 (NR 3)	NR	Yes
Cutaneous involvement	7/7 (NR 2)	2/5	No
Cardiac involvement	4/5 (NR 4) Ventricular fibrillation; right heart failure (after resuscitation); severe cardiac insufficiency; viral myocarditis (at autopsy)	1/5 Dilated cardiomyopathy then heart failure and transplantation	Yes Severe cardiac insufficiency (during infection), persistent left ventricular dysfunction

Abbreviations: MRI, magnetic resonance imaging; NR, none reported.

[a]Holling et al. (2022).

[b]Hsieh et al. (2022) (not in table) highlighted two other patients with *SLC5A6* variants. The first one presented decreased immunoglobulin levels. The second one is his deceased elderly sister. No other clinical description is available.

presented a severe metabolic decompensation during an infection (pH 6.87, base excess −30 mmol/L, hypoglycemia 2.0 mmol/L, lactate 3.0 mmol/L, and ketonuria). Further metabolic investigations showed elevated plasma propionylcarnitine, elevated plasma C5-OH-carnitine, and increased urinary excretion of 3-HIA. Montomoli et al. (2023) also described a patient with intermittent lactic acidosis and elevated urinary 3-HIA. Hauth et al. (2022) went on to describe another patient who presented an acute metabolic decompensation with lactic acidosis (pH 7.1, lactate 3 mmol/L) and hypoglycemia (1.7 mmol/L). Elevated blood lactate levels are observed in case of impaired metabolization of pyruvate as reported in biotin deficiency (Hauth et al., 2022; Tankeu et al., 2023). Metabolic assessments also showed slightly elevated urinary 3-HIA associated to elevated plasma C5-OH-carnitine, which is classically seen in biotinidase deficiency (Hauth et al., 2022; Tankeu et al., 2023). Urinary excretion of 3-HIA has been demonstrated to be an early and sensitive indicator of marginal biotin deficiency (Mock et al., 2011). One single study about SMVT deficiency recorded biotin blood values that were normal under parenteral alimentation (Subramanian et al., 2017). Schwantje et al. (2019) reported a mild decrease in biotinidase activity that remained normal in our patient. These observations support ours and we propose that the persistence of elevated and isolated urinary levels of 3-HIA could be a red flag suggesting testing for inborn errors of metabolism as biotinidase, holocarboxylase synthetase, or SMVT deficiencies (Tankeu et al., 2023).

SMVT deficiency has been so far described as acute life-threatening heart failure in only one patient. Montomoli et al. (2023) reported a patient with a severe left cardiac dysfunction occurred at 2 years and 6 months of age with a recovery under a multivitamin treatment including biotin (120 µg IV and 5 mg oral) and pantothenic acid 30 mg IV. In our case, we observed a complete cardiac recovery under bi-vitamin therapy (biotin 15 mg and pantothenic acid 100 mg). Our brother's patient also died at the age of 8 months from unexplained multisystemic decompensation and cardiac dysfunction—although, unfortunately, there is no genetic material available for him to confirm if he had the same condition. Two other patients with cardiac dysfunction have been recorded in the literature. The first sibling in the Byrne et al. (2019) study suffered from right heart failure but was diagnosed at autopsy. Authors thought it could be secondary to pre-mortem cardiopulmonary resuscitation. Another patient described by Holling et al. (2022) had a mild dilated cardiomyopathy at first but quickly developed progressive heart failure requiring heart transplantation. The pathophysiological mechanisms of cardiac dysfunction in SMVT defects remain to be elucidated. Conversely, there have been no reports of cardiac dysfunction in patients with biotinidase deficiency, even in case of metabolic decompensation (Said, 2012; Saleem & Soos, 2023). In a condition of biotin deficiency, Pacheco-Alvarez et al. (2004) discovered that SMVT expression was upregulated in brain tissue but downregulated in liver and kidney tissues. Interestingly Velázquez-Arellano et al. (2008) suggested that the same upregulation might occur in heart tissue. However, despite a biotin-deficient diet, rats in their study retain a residual activity of biotin-requiring cardiac carboxylases that maintain heart function. In SMVT defect, the absence of the transporter and the associated lack in pantothenic acid and α-lipoic acid could lead to a deeper metabolic deprivation.

Our literature review of SMVT defect symptomatology shows a wide range of symptoms. We therefore suggest testing urinary organic acids in cases of unexplained neurologic symptoms, cardiogenic or metabolic decompensation, and unexplained immune deficiency. In the presence of an isolated increased urinary 3-hydroxyisovaleric acid excretion in the absence of markedly reduced biotinidase activity, we suggest sequencing of the *SLC5A6* gene. We also recommend prompt supplementation with high doses of biotin and pantothenic acid, while awaiting the results of *SLC5A6* sequencing, as this condition can be life-threatening and high doses of these water-soluble vitamins appear to be harmless.

Subramanian et al. (2017) and Hauth et al. (2022) have already described an important and remarkable effect of high-dose vitamin therapy with biotin and pantothenic acid on neurodevelopment, weight and growth catch-up, gastro-intestinal symptoms diminution and immunoglobulin levels, and phospho-calcic balance normalization. However, Byrne et al. (2019) described a pair of siblings presenting a profound neurocognitive regression. The first sibling died subsequently to an acute gastro-intestinal hemorrhage. Vitamin supplementation started 6 years after onset in second sibling, following genetic diagnosis, led to neurocognitive improvement but no normalization. Schwantje et al. (2019) also described a patient with previous cognitive regression and persistent neurodevelopmental delay after bi-vitamin supplementation but with a lower biotin dose. With regard to our patient, we started biotin supplementation at 10 mg/day at the time of the second metabolic decompensation and adjusted the dose to 15 mg/day with the addition of 100 mg/day of pantothenic acid within 2 months of the first metabolic decompensation resulting in rapid neurodevelopmental and growth catch-up and complete normalization of cardiac function at the 3-months follow-up. Early initiation of vitamin treatment may have helped in her impressive clinical evolution. The optimal dose of vitamin

supplementation has still to be defined. Specific treatment regimens are currently based on the regimen published by Subramanian et al. (2017) and the regimen used in biotinidase deficiency (Saleem & Soos, 2023; Tankeu et al., 2023). Holling et al. (2022) have treated their patients with specific motor neuropathies with higher doses of biotin, pantothenic acid, and α-lipoic acid leading to motor improvement. Those patients were older than the others described in literature and no information about specific adverse effects of high doses of these vitamins was reported in their study. Subramanian et al. (2017) hypothesized that, in the absence of a functional SMVT, clinical effects of high-dose vitamin supplementation could be explained by simple transmembrane diffusion resulting in adequate intracellular concentrations of those vitamins. The impact of α-lipoic acid in SMVT deficiency vitamin therapy is unclear as its use was not tested in every regimen. In our patient's case, due to unavailability, α-lipoic acid took 4 months to obtain and as it tasted sour, she quickly refused it.

Previous literature shows homozygous or compound heterozygous variants in *SLC5A6* with at least one of the variants which results in partially functional SMVT. Our patient inherited a homozygous missense variant in the context of family consanguinity. We suggest that this homozygous variant could be associated with a more severe dysfunction of the SMVT. Conversely, Holling et al. (2022) reported a cohort of patients with motor neuropathies without any of the other symptoms described in patients with a multisystemic phenotype of SMVT deficiency. This could be explained by the presence of less severe variants in *SLC5A6* responsible for a less dysfunctional SMVT and a milder phenotype of the disease.

5 | CONCLUSION

Our case report of a defect in the sodium-dependent multivitamin transporter (SMVT) due to a homozygous variant in *SLC5A6* gene highlights life-threatening events with severe immunodeficiency, metabolic acidosis, and profound cardiac dysfunction triggered by infectious diseases and the successful clinical response on early vitamin supplementation. Increased and isolated excretion of urinary 3-hydroxyisovaleric acid may suggest, in the absence of markedly reduced biotinidase activity, a deficiency of the symporter SMVT. Prompt supplementation with high doses of biotin and pantothenic acid should be initiated while awaiting results of *SLC5A6* sequencing as this condition may be life-threatening. Further studies are still needed to better understand the pathophysiological processes involved in the clinical spectrum of this disease including the cardiac phenotype.

AUTHOR CONTRIBUTIONS

F.-X. Van Vyve: Data collecting, literature review, writing-original draft. N. Mercier: Conceptualization, neuropediatric follow-up, writing-original draft. J. Papadopoulos: Intensive care point of view, writing-review and editing. H. Dessy: Cardiac involvement and follow-up, writing-review and editing. C. Heijmans: Hematologic involvement and follow-up, writing-review and editing. O. Monestier: Molecular analysis, writing-review and editing. J. P. Dewulf: Metabolic studies, writing-review and editing. D. Roland: Genetic studies, project administration, coordination, writing-review and editing.

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CONFLICT OF INTEREST STATEMENT

No conflict of interest.

DATA AVAILABILITY STATEMENT

Data available in article supplementary material. François-Xavier Van Vyve and Nathalie Mercier have full access to the patient's data and are responsible for the integrity of the data.

ETHICS STATEMENT

We obtained the consent of the child's parents for the publication of the child's report.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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