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CLINICAL REPORT

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Elevated holo-transcobalamin in Gaucher disease type II: A case report

Suelen Porto Basgalupp[1,2,3] | Karina Carvalho Donis[4] | Marina Siebert[2,5] | Filippo Pinto e Vairo[6,7] | Osvaldo Artigalas[8] | Louise L. de Camargo Pinto[9] | Sidney Behringer[10] | Ute Spiekerkoetter[10] | Luciana Hannibal[10] | Ida Vanessa D. Schwartz[1,2,4,11]

[1]Postgraduate Program in Medical Sciences, School of Medicine, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil

[2]Basic Research and Advanced Investigations in Neurosciences (BRAIN) Laboratory, Experimental Research Center, Hospital de Clínicas de Porto Alegre (HCPA), Porto Alegre, Brazil

[3]Hospital Moinhos de Vento, Porto Alegre, Brazil

[4]Medical Genetics Service, Hospital de Clínicas de Porto Alegre (HCPA), Porto Alegre, Brazil

[5]Unit of Laboratorial Research, Experimental Research Center, Hospital de Clínicas de Porto Alegre (HCPA), Porto Alegre, Brazil

[6]Center for Individualized Medicine, Mayo Clinic, Rochester, Minnesota

[7]Department of Clinical Genomics, Mayo Clinic, Rochester, Minnesota

[8]Hospital da Criança Conceição, Grupo Hospitalar Conceição (GHC), Porto Alegre, Brazil

[9]Hospital Infantil Joana de Gusmão, Florianópolis, Brazil

[10]Laboratory of Clinical Biochemistry and Metabolism, Department of General Pediatrics, Adolescent Medicine and Neonatology, Faculty of Medicine, Medical Center, University of Freiburg, Germany

[11]Department of Genetics, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil

Correspondence
Luciana Hannibal, Laboratory of Clinical Biochemistry and Metabolism, Department of General Pediatrics, Adolescent Medicine and Neonatology, Medical Center, University of Freiburg, Mathildenstr. 1, Freiburg 79106, Germany.
Email: luciana.hannibal@uniklinik-freiburg.de

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Abstract

Gaucher disease (GD), one of the most common lysosomal disorders, is caused by deficiency of β-glucocerebrosidase. Based on the presence and severity of neurological complications, GD is classified into types I, II (the most severe form), and III. Abnormalities in systemic markers of vitamin B_{12} (B_{12}) metabolism have been reported in GD type I patients, suggesting a higher prevalence of B_{12} deficiency in these patients. A 2-month-old male with GD type II was admitted to the hospital presenting jaundice, hepatosplenomegaly, and ichthyosis. At admission, cholestasis and ascites, abnormal liver function enzymes, prolonged prothrombin time, and high levels of B_{12} were confirmed. Analysis of biomarkers of B_{12} status revealed elevated B_{12} and holo-transcobalamin (holo-TC) levels. The B_{12} profile found in our patient is the opposite to what is described for GD type I patients. Holo-TC may increase in inflammatory states or due to liver diseases. In GD, the accumulation of glucocerebroside

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; B_{12}, vitamin B_{12}; Cbl, cobalamin; CNS, central nervous system; ERT, enzyme replacement therapy; GCase, β-glucocerebrosidase; GD, Gaucher disease; Holo-TC, holo-transcobalamin; MMA, methylmalonic acid; NGS, next-generation sequencing; SRT, substrate reduction therapy; tHcy, total homocysteine.

may be a trigger that initiates a systemic inflammatory reaction, characterized by macrophage activation. We suggest higher levels of holo-TC could be associated with a more severe (neuronopathic) GD, and be a biomarker of GD type II.

KEYWORDS
biomarker, Gaucher disease type II, holo-TC, macrophage

1 | INTRODUCTION

Gaucher disease (GD) is a lysosomal disorder with autosomal recessive inheritance. The disease is caused by biallelic pathogenic variants in the *GBA1* gene that result in β-glucocerebrosidase (GCase) deficiency. More rarely, GD is caused by variants in the *PSAP* gene that encodes saposin C. Enzyme deficiency leads to the accumulation of glucocerebroside substrate in tissues resulting in the formation of Gaucher cells that harm the regular function of specific organs (Sidransky, 2004). GD is classified into three types based on the absence (type I) or presence and severity (types II and III) of involvement of the central nervous system (CNS).

GD type I corresponds to more than 90% of GD cases in the Western World and it is characterized by high variability in the progression and severity of the symptoms. The most common manifestations are splenomegaly, anemia, thrombocytopenia, and bone changes (Zimran et al., 2018). GD type II is the rarest and the most severe type, being characterized by early onset of systemic clinical signs and involvement of the CNS, resulting in death within the first 2 years of life (Sidransky, 2004; Stirnemann et al., 2017). The predominant clinical features of GD type II are developmental delay, ocular problems such as strabismus, vertical gaze paralysis, opisthotonus, and spasticity; fetal hydrops, congenital ichthyosis, and neonatal cholestasis may also occur (Goker-Alpan et al., 2003). GD type III is an intermediate form of GD in terms of severity in that it compromises CNS functions more slowly and gradually compared to GD type II (Sidransky, 2012). Individuals with GD type III have systemic involvement and neurological impairment that may manifest over time usually accompanied by epilepsy, ataxia, vertical and horizontal gaze paralysis, and dementia. Also, patients with GD type III may present valvular heart disease, especially individuals carrying the D409H variant (Hruska, LaMarca, Scott, & Sidransky, 2008).

Patients with GD, especially type I, are usually treated with enzyme replacement therapy (ERT) or substrate reduction therapy (SRT). However, specific treatment is not indicated for patients with GD type II due to the severity of the disease and limited prognosis (Beutler, 2006), except in cases of symptomatic patients who could receive treatment such as gastrostomy tube, tracheostomy, and antiepileptic medications (Lal et al., 2020).

Assessment of plasma vitamin B_{12} (B_{12}) concentration, homocysteine (Hcy), and methylmalonic acid (MMA) in untreated GD type I patients retrieved no differences compared to ethnicity-matched health controls, although this could have been due to pre-selection of patients with mild phenotypes (Gielchinsky et al., 2001). Results from early studies showed elevation of plasma holo-transcobalamin (holo-TC) in GD type I patients that did not correlate with the concentration of B_{12} or other B_{12}-transport protein (Gilbert & Weinreb, 1976; Zimran, Gelbart, Westwood, Grabowski, & Beutler, 1991). In contrast, there is a lack of reports on B_{12} status in GD types II and III.

Previous studies in other disorders with lysosomal involvement provided insights into disturbed cobalamin metabolism (Stockler et al., 2014; Zhao, Li, Ruberu, & Garner, 2015). A patient with a defective endocytic pathway due to a variant in *ZFYVE20* gene exhibited elevated holo-TC, along with elevated plasma Hcy, elevated urinary MMA and low plasma B_{12} (Stockler et al., 2014). Cobalamin tracing studies in a mouse model of Alzheimer disease and in cultured glioblastoma cells showed that β-amyloid buildup in lysosomes results in trapping of cobalamin in the organelle with possible onset of functional cobalamin insufficiency (Zhao et al., 2015). Patients with primary defects in lysosomal transporters of B_{12} such as LMBD1 (methylmalonic aciduria and homocystinuria, cblF type) and ABCD4 (methylmalonic aciduria and homocystinuria, cblJ type) present poor growth, feeding difficulties, and mild to severe developmental delay (Coelho et al., 2012; Fettelschoss et al., 2017; Gailus et al., 2010; Rosenblatt, Hosack, Matiaszuk, Cooper, & Laframboise, 1985; Rutsch et al., 2009). The above described abnormalities in plasma biomarkers of B_{12} status both in GD patients and in other lysosomal pathologies, raise the question as to whether cellular handling of this micronutrient is sensitive to impaired lysosomal storage (Hannibal et al., 2017). However, studies performed on skin fibroblasts from healthy controls and from GD types I, II, and III suggested that cellular utilization of B_{12} is preserved in this cell type (Basgalupp et al., 2020). This finding along with literature reports on elevated plasma biomarkers point to the need to further investigate how impaired lysosomal storage influences B_{12} metabolism in different cell types as well as its partition between biological compartments (plasma versus cells).

B_{12} deficiency may be caused by nutritional deficiency or defects that disrupt B_{12} absorption, its processing or trafficking pathways and it may lead to the accumulation of total homocysteine (tHcy) and MMA (Hannibal et al., 2016; Hannibal et al., 2017). Unfortunately, studies of B_{12} status incorporating all four biomarkers, namely, plasma B_{12}, holo-TC, Hcy, and MMA in patients with GD types II and III, representing severe disease variants, are not available. In the past, elevated plasma B_{12} was identified in a GD type II patient followed by our group (data not shown). However, the assessment of B_{12} profile could not be completed in this patient. Herein, we report a complete assessment of B_{12} status on a new case of GD type II. The patient presented increased plasma concentrations of B_{12} and its transporter

protein holo-TC, but without abnormalities of metabolite biomarkers Hcy and MMA. Disease severity and the presence of elevated holo-TC support earlier proposals that the bioactive fraction of B_{12} in circulation, represented by holo-TC, may serve as an additional biomarker of GD severity.

2 | CASE REPORT

A two-month-old male born to a non-consanguineous couple, with no history of perinatal insult, presented jaundice at 10 days of age. The maternal and paternal ages were 26 and 27 years old, respectively. He was vaginally delivered at 39.5 weeks of gestation without any complication. Prenatal follow-up was uneventful. The mother denied previous or gestational diseases, use of medications, alcohol, and tobacco during pregnancy. Apgar score was six at the first minute and eight at the fifth minute. Body weight was 2460 grams (p5), length was 47 cm (p10), and head circumference was 32 cm (p5). The patient was discharged from the hospital at 2 days of age. Newborn screening showed increased galactose 13.6 mg/dl (RV up to 10 mg/dl) on a dried blood spot sample and confirmatory testing ruled out galactosemia.

At 10 days of age, he was admitted to a pediatric Hospital due to hyperbilirubinemia, cholestasis, septicemia, and thrombocytopenia. At 53 days of age, he had a new episode of sepsis. At 60 days of age, he was transferred to our Hospital. The patient presented jaundice, ichthyosis, opisthotonos to manipulation, and did not follow stimuli with the eye. Ophthalmologic evaluation was unremarkable. Liver and spleen were palpable in the iliac fossa. Body weight, length, and head circumference were 3340 g ($p < 3$), 48.5 cm ($p < 3$), and 34.5 cm ($p < 3$), respectively.

Initial laboratory tests showed platelets of $41 \times 10^3/\mu l$ (RV = 210–650 $\times$ $10^3/\mu l$), total bilirubin at 20.5 mg/dl (RV = up to 1 mg/dl), direct bilirubin at 15.67 mg/dl (RV = up to 0.3 mg/dl), aspartate transaminase (AST) at 483 U/L (RV = 15–40 U/L), alanine transaminase (ALT) at 234 U/L (RV = 10–40 U/L), and prolonged prothrombin time activity (48.3%; RV = more than 70%). Abdominal ultrasound confirmed hepatosplenomegaly and portal vein thrombosis with portal hypertension. Echocardiogram was normal. Screening for infectious diseases, including cytomegalovirus and rubella was negative. Chitotriosidase activity was at 4987 nmol/h/ml of protein (RV = 8.8–132 nmol/h/ml) and GCase activity in leukocytes was 0.65 nmol/h/mg of protein (RV = 10–45 nmol/h/mg of protein). *GBA1* genotyping was p.[Leu483Pro;Glu365Lys];[Leu483Pro;Ala495Pro;Val499=](L444P + E326K/Rec*Nci*I) confirming the diagnosis of GD type II.

The levels of ferritin, tHcy and B_{12} were at 4175 ng/ml (RV = 30–400 ng/ml), 8.3 μmol/L (RV = 5–15 μmol/L), and 1459 pg/ml (RV = 211–946 pg/ml), respectively. The blood level of MMA was normal (0.18 μmol/L; RV = 0.16–0.60 μmol/L).

A second blood sample was analyzed and high levels of B_{12} and of holo-TC (the bioactive form of B_{12} in circulation; >128 pmol/L; RV = 35–50 pmol/L) were confirmed. The patient had never received vitamin supplementation, although he was fed with an infant formula at 27 days of age. A gene panel, including 16 genes involved in iron metabolism, identified 3 heterozygous non-pathogenic variants in genes associated with hemochromatosis type I, neuroferritinopathy, and iron-refractory iron deficiency anemia (p.Ser65Cys in *HFE*, p.Gln4His in *FTL*, and p.Val736Ala in *TMPRSS6*). After discharge at 66 days of life, he was put on hospice care at home and died at 76 days of life.

A literature search retrieved only a few studies reporting biomarkers of B_{12} status in patients with GD and other lysosomal disorders (Table 1).

3 | DISCUSSION

GD type II, or acute neuronopathic form, is the most severe form of the disease, which presents neurological involvement within the first months of life, followed by death within the first years of life (Stone et al., 2000). It comprises about 1% of all GD cases and affects all ethnicities. Perinatal-lethal GD is exceptionally rare. While GD type II is generally associated with specific mutations in *GBA1*, there is also significant genotypic heterogeneity and genotype–phenotype associations are not conclusive (Eblan, Goker-Alpan, & Sidransky, 2005).

Bhutada, Pyragius, Petersen, Niemann, and Matsika (2018) reported a case of Perinatal-lethal GD prenatally presenting thrombocytopenia, transfusion refractory severe anemia, and non-immune fetal hydrops. In this case report, the genetic analysis revealed that the fetus was homozygous for the Rec*Nci*I variant in the *GBA1* which usually causes severe phenotypes (Bhutada et al., 2018). This variant occurs due to recombination events between *GBA1* and its highly homologous pseudogene located 16 kb downstream, known as *GBAP* (Tayebi et al., 2003). Genetic analysis for GD can be challenging as several mutations originate from the pseudogene sequence, so it is essential to differentiate between *GBA1* and *GBAP* sequences especially when using next-generation sequencing (NGS) platforms for the diagnosis of GD.

In contrast to B_{12} deficiency, pathophysiology and clinical consequences of high B_{12} serum levels are not often reported. However, an increasing number of studies show that increase in plasma B_{12} and/or holo-TC is associated with a variety of pathological outcomes including liver diseases, cancer, and autoimmune disorders (Andrès, Serraj, Zhu, & Vermorken, 2013; Arendt, Farkas, Pedersen, Nexo, & Sørensen, 2016; Arendt, Farkas, Pedersen, & Sørensen, 2017; Arendt & Nexo, 2013; Carmel, 1975; Deneuville et al., 2009; Oh, Lee, Eo, Yoon, & Han, 2018; Rahbek, Scheller, Nybo, & Ryg, 2018; Solomon, 2016; Zulfiqar, Sebaux, Dramé, & Andres, 2017).

Chiche et al. (2008) found association between high levels of B_{12} and the presence of blood malignancies, suggesting an investigation for possible blood disorder in cases of elevated B_{12} (Chiche et al., 2008). Similarly, Deneuville et al. (2009) reported association between high levels of B_{12} and liver diseases such as cirrhosis and hepatocellular carcinoma (Deneuville et al., 2009). Furthermore, high levels of B_{12} in inflammatory disease may be linked to an increase in holo-TC during the acute phase of inflammation (Solomon, 2007).

TABLE 1 Studies reporting biomarkers of B_{12} status in patients with GD and other lysosomal disorders

Authors	Title of manuscript	Disease and No. of participants	Reported findings			
			Vitamin B_{12}	Holo-TC	Hcy	MMA
This study	Elevated holo-TC in Gaucher disease type II: a case report	GD type 2, n = 1	↑	↑	≈	≈
Gilbert & Weinreb, 1976	Increased Circulating Levels of Transcobalamin II in Gaucher's Disease	GD type 1, n = 15	≈	↑	ND	ND
Biegstraaten et al., 2010[a]	Peripheral neuropathy in adult type 1 Gaucher disease: a 2-year prospective observational study	GD type 1 Polyneuropathy n = 17 No polyneuropathy n = 86	≈	ND	≈	≈
Gielchinsky et al., 2001[b]	High prevalence of low serum vitamin B_{12} in a multi-ethnic Israeli population	GD type 1, n = 89 Healthy controls = 122	≈↓	ND	≈	≈
Stockler et al., 2014	Single point mutation in Rabenosyn-5 in a female with intractable seizures and evidence of defective endocytotic trafficking	Rabenosyn-5 deficiency, n = 1	≈↓	↑	≈	≈↑
Zhao et al., 2015	Impaired lysosomal cobalamin transport in Alzheimer's disease	Cobalamin trapping in lysosomes (neuroblastoma cell line and mouse model of Alzheimer's disease)	ND	ND	ND	ND

Note: ↓ Below normal reference range. ↑ Above normal reference range. ≈ Within normal reference range. ND: not determined.
[a]While both within the reference range, Hcy and MMA concentrations were higher in patients with neuropathy compared to those without neuropathy ($p = 0.013$ and $p = 0.001$, respectively; 95% confidence).
[b]Both healthy controls and GD type 1 had a marked incidence of low B_{12}. Differences between groups were not statistically significant.

Fehr and De Vecchi (1985) have shown that holo-TC is a marker for macrophage proliferation in malignant and reactive macrophage proliferation (Fehr & De Vecchi, 1985). In GD, the accumulation of glucocerebroside may be a trigger that initiates a systemic inflammatory reaction, characterized by macrophage activation (Kacher & Futerman, 2006) and it could explain the results of elevated plasma B_{12} and holo-TC for our patient.

Plasma B_{12} and holo-TC concentrations could be elevated during infant formula intake. However, our patient had higher than expected levels, since the formula ingested contains low levels of B_{12} (around 1.4 μg per 100 g), which does not explain the increase in these biomarkers in our patient.

It is possible that holo-TC could be exploited as a secondary biomarker of disease severity in GD. It would be important to test this hypothesis in larger cohorts of GD patients and also in other diseases characterized by macrophage activation. This would evaluate marker specificity toward disease-type versus macrophage activation as the driver of elevated holo-TC.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

Suelen Porto Basgalupp carried out the study conception, data collection and the manuscript writing; Karina Carvalho Donis collected data and assisted in manuscript preparation; Marina Siebert revised the manuscript; Filippo Pinto e Vairo made the clinical evaluation of the patient and performed the critical appraisal of manuscript content; Osvaldo Artigalas made the clinical evaluation of the patient; Louise L. de Camargo Pinto evaluated the previous patient investigated; Sidney Behringer performed and analyzed the biochemical experiments; Ute Spiekerkoetter designed experiments and revised the manuscript; Luciana Hannibal designed the experiments, analyzed data, supervised the writing, and revised the manuscript; Ida Vanessa D. Schwartz designed the experiments, supervised the writing and revised the manuscript. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

ORCID

Suelen Porto Basgalupp https://orcid.org/0000-0002-3274-8801
Luciana Hannibal https://orcid.org/0000-0002-0911-5758

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