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Major Metabolic Changes and Nutritional Implications in Gaucher's Disease: A Mini-Review

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ABSTRACT

Gaucher's Disease (GD) is caused by gene mutations inducing a deficiency in the production of glucocerebrosidase or saposin C (a cofactor). Glucocerebrosidase is an important catalyst of the hydrolysis of glucosylceramide into ceramide and glucose. This leads to the accumulation of sphingolipids in macrophages (called Gaucher cells) in several tissues, especially in the reticuloendothelial system, resulting in a spectrum of clinical manifestations, including hepatosplenomegaly, anemia, thrombocytopenia and bone crisis. In GD, cytokines are also released and major functional changes occur affecting the iron, calcium and insulin metabolism, with serious consequences for the patient's energy balance.The purpose of this paper is to provide health professionals with a summary of the major metabolic and nutritional changes observed in GD patients.

INTRODUCTION

Mutations in the glucocerebrosidasegene (GBA, located in the q21 region ofchromosome 1) [1] cause a potentially severe deficiency of thelysosomal enzyme glucocerebrosidase (GCase; glucosylceramidase or acid β-glucosidase; EC: 4.2.1.25) [2]. GCasecatalyzes the hydrolysis of glucosylceramide (GlcCer) into ceramide and glucose. Low GCaseactivity leads to the accumulation of glucosylceramide and glucosylsphingosine (GlcSph)in the lysosomes of macrophages in several tissues, especially in the reticuloendothelial system [3-5]. These cells are commonly referred to as Gauchercells. More than 300 mutations in the GBA gene have been described [6]. Though this is rarely the case, Gaucher's Disease (GD) may also be caused by a deficiency of saposin C (aGCase activator) [5].

The GD phenotype is expressed in different degrees from one individual to another, but three classic forms can be distinguished clinically based on neurological involvement: non-neuropathic (GD1), acute neuronopathic (GD2), and chronic neuronopathic (GD3) [7], the prevalence of which is 91.5%, 1.2% and 7.3%, respectively [8]. GD1may be asymptomatic or display a range of clinical manifestations, including hepatosplenomegaly, anemia, thrombocytopenia, bone crisis, osteonecrosis, diminished bone density, fractures and (less commonly) interstitial lung disease [9,10].

The boundaries between the threetypes are not clear due to the wide spectrum of symptoms and occasionally late-onset neurological manifestations (such as Parkinson's

disease and peripheral neuropathy) observed in GD1. In fact, distinguishing GD types based on a single parameter can be very challenging. Therefore, some researchers prefer to view GD as a continuum of phenotypes [11]. Thoughpanethnic, GD is particularly prevalent among Ashkenazi Jews (1:400-800 births). In comparison, the incidence in the general US population is 1:40,000-60,000 births [12]. GD severitymay be determinedby the level organ involvement. This requires careful analysis under malleable clinical criteria, laboratory testing and imaging, as described by Zimran and collegues [13]. Currently,the two most effective treatments for GD are Enzyme Replacement Therapy (ERT) and Substrate Reduction Therapy (SRT). Both approaches effectivelycontrol visceral, hematological and bone manifestations, there by improving patients' quality of life [14].

LYSOSOMES AND CHANGES IN GD

The role of lysosomes in GD has been studied since 1968 [15] to better understand the observed abnormal catabolism of GlyCer and subsequent accumulation inside lysosomes [16,17]. Despite considerableadvances in the currentknowledge of the genetic, molecular and biochemical aspects of GD, it is not fully understood how GlcCer accumulation in lysosomes causes disease at the cellular level [18], nor how metabolic changes influence liver metabolism and cardiovascular risk, both before and during long-term ERT/SRT [19].

In addition to lysosomal storage diseases, acquired conditions (e.g., obesity and metabolic syndrome associated with insulin resistance and unhealthy dietary habits and sedentary lifestyle) are known to be strongly associated with lysosomal dysfunction and subsequent metabolic imbalance [19]. Recent studies suggest that compounds of the glycosphingolipid pathways acting as potential secondary messengers and directly or indirectly affecting intra- and intercellular relationships are involved in a range of pathologies, including increased insulin resistance and abnormal lipid trafficking [20].

HYPERMETABOLISM IN GD

GD is characterized by systemic inflammation and increased energy expenditure, probably related to the activation of macrophages and the production of proinflammatory cytokines [19,21]. Hypermetabolism secondary to systemic inflammation in GD1 is partly reversed by ERT/SRT [21],sometimes with a subsequent ~5% ponderal gain, followed by weight stabilization.This increase in weight does not appear to be directly related to duration, doseor response to treatment [22].Other than that, ponderal gain is usually due to aging, unhealthy dietary habits and/or sedentary lifestyle, as observed in the general population [19]. Furthermore, in addition to causing glucosylceramide and glucosylsphingosine to accumulate in the lysosomes of macrophage cells and visceral organs, glucocerebrosidase deficiency has also been shown to promote mitochondrial dysfunction in several cellular and mouse models of GD [23].

The association between GD (a lysosomal storage disorder) and insulin resistance (a membrane-related disorder) was first pointed out over 20 years ago, but the mechanisms involved have still not been fully explained [24]. The hypothesized association between increased insulin resistance and overweight in patients receiving ERT was not confirmed in a cross-sectional study conducted in Turkey [19], but GD is believed to be associated with peripheral insulin resistance, possibly through the influence of glycosphingolipids on insulin receptor function [25]. Prior to receiving ERT, Dutch GD1 patients had a lower than expected prevalence of type 2 Diabetes Mellitus (DM), despite the abnormal insulin resistance. However,once started on ERT,weight increased and the prevalence of DM rose to the level of the general population. It is not clear whether this phenomenon extends to other GD1 populations (e.g., Ashkenazi Jews) with other, non-GD-related risk factors for DM [26].

The accumulation of GlyCerin GD influences lipid metabolism and intracellular concentrations and transport of gangliosides, phosphatidylcholine and sphingomyelin, there by altering lipid and lipoprotein plasma levels. In addition to these changes, apolipoprotein abnormalities have also been reported [27]. The association between GD and reduced levels of Low-Density Lipoprotein (LDL), High-Density Lipoprotein (HDL), Apolipoproteín B (ApoB) and Apolipoprotein A1 (ApoA1) may be explained by the upregulation of LDL and HDL catabolism due to GD-related impairment of macrophage function [28,29]. On the other hand, the plasma levels of triglycerides and Apolipoprotein E (ApoE) are reportedly elevated in GD patients [28,30].

HDL levels increase rapidly with ERT/SRT but remain lower in GD patients than in healthy controls, even after years of

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treatment. There is no evidence to suggest this atherogenic lipid profile is associated with increased cardiovascular risk in GD patients, but so far very few prospective studies has been conducted [19,31]. The tendency of severe GD patients to have extremely low HDL levels (and the ability of ERT to elevate them) has led some authors to propose HDL as an inexpensive and reliable adjunctive biomarker for the diagnosis and monitoring of GD. However, no study has found significant correlations between low HDL levels and risk of atherosclerosis, ischemic heart disease, hypertension or DM [32].

HYPERFERRITINEMIA IN GD

Iron (probably resulting from erythrophagocytosis) is stored as ferritin in Gaucher and non-Gaucher macrophages, especially in the spleen, bone marrow and liver (Kupffer cells). Iron overload likely increases the risk of cancer, Metabolic Syndrome (MetS) and Neurogenerative Disease [33]. In such cases, hyperferritenemia may reach the levels observed in Hereditary Hemochromatosis (HH), but the transferrin saturation percentage is usually normal in GD, as opposed to HH. There is no evidence for iron-associated cardiac or pancreatic disease in GD, but iron storage in osteoblasts is believed to contribute to osteopenia.

The consequences of iron accumulation depend on individual differences in the classic and alternative pathways of macrophage activation. Thus, elevated ferritin levels may be used as a GD activity marker. However, it should be kept in mind that high ferritin levels in GD patients sometimes masks iron deficiency resulting from conditions like heavy menstrual or gastrointestinal bleeding.The truth is that, while significant advances have occurred in diagnosis and therapy, many basic aspects of GD remain poorly understood [34].

BONE LESIONS ASSOCIATED WITH GD

Metabolic changes associated with the formation and remodeling of bones are evident in GD. Clinical manifestations are due to medullary infiltration of macrophages filled with glucocerebrosides which act directly by way of mechanical pressure and indirectly through cytokine-induced inflammation, there by modulating osteoblastic and osteoclastic activity. These changes include abnormal bone remodeling, osteopenia, osteoporosis, lytic lesionsand avascular necrosis. Among the clinical manifestations are bone pain, bone crisisand pathological fractures, leading to disability and progressive loss of quality of life [35,36]. Bone mineral density may also be influenced by the genetic variability of the Vitamin D Receptor (VDR) gene, the Estrogen Receptor (ESR1) gene, the collagen 1A1 gene, the Calcitonin Receptor Gene (CAL), the Osteoprotegerin Gene (TNFRSF11B; OPG) or the RANK gene (TNFRSF11A) across populations of GD patients [37]. Serum calcium (potentially serum phosphorus) and vitamin D levels should be monitored because vitamin D deficiency appears to be more common in GD than in the general population, and supplementation is highly recommended when the level of calcifediolis <75 nmol/L [36].

More research is needed to clarify changes in bone metabolism in GD. According to some authors, prior to the introduction of enzyme therapy, bone disease tended to worsen in patients submitted to splenectomy [38,39]. ERT has improved clinical symptoms and reduced the severity of bone disease and the need for splenectomy in GD patients [33,40,41].

METABOLIC SYNDROME DURING TREATMENT FOR GD

Some GD patients undergoing long-term ERT develop MetS. However, due to the scarcity of detailed pre-treatment studies, a causal link has not yet been established [26]. In arecent Brazilian cross-sectional study,MetSwas a frequent finding in GD1 patients on ERT. Interestingly, MetS was positively associated with BMI, waist circumference, triglycerides, insulin and leptin levels, and negatively associated with adiponectin levels [22]. No cause-of-death information was available for approximately half the GD cases reviewed, but ERT/SRT appears to reduce mortality from visceral, pulmonary and skeletal complications and increase mortality from cardiovascular and cerebrovascular conditions [42]. Further studies are necessary to clarify whether the reported increase in cardiovascular mortality is due to GD-related metabolic disorders or the result of reduced mortality from classical GD-related complications during ERT/SRT in patients reaching or surpassing the actuarial life expectancy [11].

In addition, GD patients are, like other adults, exposed to risk factors associated with unhealthy dietary habits and sedentary lifestyle. Aging GD patients may therefore be expected to acquire health problems prevalent in the elderly, such as cardiovascular morbidity, malignancy, neurodegenerative disease, dementia, Chronic Obstructive Pulmonary Disease

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(COPD) and chronic liver and kidney disease. Finally, we believe more research is needed to clarify how ERT/SRT and lifestyle affect metabolic and nutritional parameters in GD and long-term prognosis. Among other things, metabolic studies can help develop disease activity markers for use in both treatment and surveillance and provide a more accurate picture of the natural history of GD.

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