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Combined beta-glucosylceramide and ambroxol hydrochloride in patients with Gaucher related Parkinson disease: From clinical observations to drug development

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ABSTRACT

Both patients with non-neuronopathic Gaucher disease (GD) and heterozygous *GBA* mutation carrier are at increased risk for Parkinson disease (PD). The risk for PD in these groups does not linearly increase with glucosylceramide (GC) accumulation or with acid β-glucocerebrosidase (GCase) activity. This observation, together with other clinical systemic observations raises the possibility that extra-cellular GC actually has beneficial, anti-inflammatory, properties. Based on this hypothesis, we suggest here that the administration of supplementary oral GC to *GBA* carriers at risk for PD may slow inflammatory-driven secondary neuronal death. Such a treatment may act synergistically in *GBA* carriers once given in combination with an agent that prevent the primary pathologic process that leads to cell death. Ambroxol hydrochloride, a pharmacological chaperone, which reduces endoplasmic reticulum (ER) stress induced by accumulation of mutant misfolded GCase could serve as such an agent. The efficacy of this combined therapy, derived from clinical observations, in vivo and in vitro studies, should be evaluated in clinical trials.

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1. Introduction

Parkinson disease (PD) is the second most common neurodegenerative disease [1]. In the absence of disease-modifying agent, current therapies are solely symptomatic. These therapies target the motor (tremor, bradykinesia, rigidity and impaired postural reflexes), psychiatric (anxiety, depression, psychosis) and to a less extent the cognitive aspects of the disease. Given the expected increased number of affected individuals with the aging of the population, there is a growing unmet need for disease modifying agents.

The association between PD and mutations in the *GBA* gene is well established. Initially, clinical observations in patients with non-neuropathic (type 1) Gaucher disease (GD) shed light on the co-occurrence of GD and PD [2]. More recent work has demonstrated an increased risk for PD among *GBA* carriers [3,4]. The increased risk for PD among mutation carriers is between 3-fold for carriers of mild *GBA* mutation (e.g. N370S) and 15-fold for carriers of more severe *GBA* mutation (e.g. L444P or 84GG) [5]. Surprisingly, the risk of developing PD in patients with GD (who have two mutated *GBA* alleles) is comparable to the risk for PD among carriers of a single *GBA* mutation [6]. Moreover, in many cases, GD patients who develop PD have a relatively mild GD that does not require enzyme replacement therapy (ERT) [7,8].

Here we review the available evidence regarding the relative risk for PD among *GBA* carriers, mild non-neuropathic GD patients and severe non-neuropathic GD patients. Based on these observations and others from *in vitro* and *in vivo* studies, we propose a novel therapeutic approach, combining β-glucosylceramide (GC) with the pharmacological chaperone ambroxol hydrochloride to slow the progression of PD or even prevent prodromal PD from developing into clinical disease.

2. Lack of correlation between '*GBA* expected mutation impact' and the risk for PD

The molecular pathway that leads from *GBA* mutation to accumulation of alpha-synuclein and neuronal death is still unclear. Two possible explanations to the pathogenicity of *GBA* mutations have been suggested. The first is the potential neurotoxicity of accumulated substrate secondary to dysfunction of the lysosomal acid β-glucocerebrosidase

Abbreviations: GD, Gaucher disease; GCase, β-glucocerebrosidase; GC, β-glucosylceramide; PD, Parkinson disease; ERT, enzyme-replacement therapy; *GBA*, glucocerebrosidase gene; GBA-EMI, *GBA* expected mutation impact; ER, endoplasm reticulum; DCs, dendritic-cells; NKT, natural killer T.

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(GCase) (8). The second is based on the accumulation of misfolded protein (the enzyme GCase) in the endoplasm reticulum (ER) leading to ER stress and cellular death [9,10].

To simplify our discussion regarding the relation between *GBA* status and the risk for PD we would like to suggest that a new term, "*GBA* expected mutation impact" (GBA-EMI) is compatible with the two suggested explanations regarding *GBA* pathogenicity in PD. In line with the first explanation (substrate neurotoxicity) GBA-EMI reflects the severity of substrate accumulation. The expected impact, in this case, will be low among carriers of mild mutations (e.g. N370S/wt), higher among these with two mild mutations (e.g. N370S/N370S) and even higher among compound heterozygous with one mild and one severe mutation (e.g. N370S/L444P). In line with the second explanation (toxic misfolded protein) GBA-EMI can be assumed to be doubled in homozygous N370S/N370S GD patients compared to heterozygous N370S/wt individuals.

Conclusion regarding GBA-EMI in GD patients with PD (GD + PD) and without PD (GDnonPD) can be drawn based on the ICGG (International Collaborative Gaucher Group) Gaucher Registry [11]. When compared with GDnonPD, GD + PD patients had later age of GD diagnosis (GDnonPD: $n = 649$, mean ± SD 31 ± 0.85 years, GD + PD: $n = 68$, 37 ± 3.8 years, $P = 0.02$), received ERT at later age (GDnonPD: $n = 564/649$, 48 years, GD + PD: $n = 54/68$, 54 years, $P < 0.01$) and were less splenectomized (GDnonPD: $n = 293/649$, 45.1%, GD + PD: $n = 20/68$, 29.4%, $P = 0.01$). Anemia was less frequent among GD + PD patients ($P < 0.01$) and other GD features (thrombocytopenia, hepatomegaly and bone disease) were not significantly different in GD + PD patients.

In the ICGG registry data, *GBA* mutation type was only partially reported. Homozygosity for mild N370S/N370S form was more frequent in GD + PD (GDnonPD: 172/438, 39.2%, GD + PD: $n = 27/59$, 45.8%). Relatively higher frequency of the mild N370S mutation in GD + PD (vs. GDnonPD) was demonstrated in another small study [12] in which it was also demonstrated that there was a tendency for lower chitotriosidase levels ($P = 0.07$) in the serum of GD + PD, reflecting milder systemic disease. These limited data, therefore, indicate that on average, GD + PD patients have lower GBA-EMI relative to GDnonPD patients. Consistent with these observations is the demonstration that ERT does not have protective effect against PD [8].

GBA-EMI is clearly lower among carriers of single mutation relatively to GD patients. In case, if GBA-EMI is the determining factor for the risk of developing PD, we would expect a much higher risk for PD among GD patients. This, however, is not the case [6]. The risks for PD in heterozygous *GBA* carriers and in GD patients are not significantly different.

To conclude, the lack of positive correlation between GBA-EMI and the risk for PD is surprising and does not sit well with a simple model of inheritance. Moreover, our clinical observations indicate that the incidence of PD among patient with the highest GBA-EMI, namely untreated type 1 compound heterozygous GD patients with one mild and mild severe mutation, is very low. Based on this, we conclude that another factor which protects individuals with high GBA-EMI from developing PD breaks this expected correlation between GBA-EMI and phenotype.

3. Possible protective effect of the GD "Lipidome"

GD patients have altered humoral and cellular immune profiles [13–15]. These immunological differences contribute to some GD manifestations such as bone resorption and a high frequency of polyclonal hypergammaglobulinemia [16]. The immunological profile of GD patients has been suggested to stem from their unique milieu of lipids [17], the "lipidome", and specifically from glycosphingolipids (GSLs), the main altered component in GD.

Lipids have been known to have interactions with a myriad of cellular processes including apoptosis, inflammation and immune response [18], and to be intimately linked to disease processes such as neurodegenerative diseases, ischemic heart diseases and congenital defects [19]. It has been speculated [17] that while elevated intracellular GSLs leads to cellular damage, elevated extracellular levels are actually beneficial. The benefit of the GD lipidome may be lost with long term ERT.

The beneficial effect of extracellular GSLs, especially β-glucocerebrosidase (GC), on a variety of diseases, especially immune-mediated conditions, is supported by several observations. A partial list includes the following observations: GD patients have a lower rate of obesity, insulin resistance and diabetes while reducing extracellular GC levels with ERT predisposes patients to all these conditions [20]. The administration of β-sphingolipids in an animal model (*Psammomys obesus*) of non-alcoholic steatohepatitis [21] or to human subjects with non-alcoholic steatohepatitis [22] has an ameliorating effect.

While patients with GD tend to have a higher prevalence of some autoimmune disorders, such as Hashimoto thyroiditis, ITP, hemolytic anemia or uveitis [23] there has been no evidence of a direct correlation between elevated autoantibodies and autoimmune diseases, and along this line, anti-DNA antibodies from GD patients have failed to induce experimental SLE in mice [24]. These patients do not develop premature atherosclerosis despite low HDL levels [25]. The GD lipidome does not expose patient to solid malignancies as large studies showing no increase in solid cancers in GD [26,27] despite the well-established connection between chronic inflammatory states and cancer. Murine model of graft-versus-host disease (GVHD) show improvement under GC treatment [28]. Finally, even acute immune-mediated phenomena, such as experimental colitis, have the potential to be treated with sphingolipids [29].

GC anti-inflammatory properties [30–37] are attributed to its potential effects on the cross talk between dendritic-cells (DCs) and natural killer T (NKT) cells [38,39]. This cross talk is relevant to brain inflammatory conditions. In the healthy brain, DCs are not found in the parenchyma but are restricted to the vascular-rich choroid plexus and meanings [40]. In neuro-inflammatory conditions, on the other hand, DCs migrate to the brain parenchyma. This pathologic process makes the application of GC relevant to PD [40].

4. The role of inflammation in the pathogenesis of PD

PD has been shown to have an intimate connection with neuroinflammatory processes [41], including the presence of activated microglia, and the presence of inflammatory cytokines in the brain of PD patients [42,43]. Inflammation in PD may be triggered by neuronal damage and loss. In vitro and in vivo studies suggested that neuromelanin spillage from dying dopaminergic neurons can serve as a potent trigger of microglial cell activation and production of pro-inflammatory cytokines [37,44]. DCs maturation is a step in this process [40].

While GC may attenuate secondary inflammatory processes that accelerate neuronal loss in PD it does not prevent the primary process leading to neuro-degeneration. In order to achieve primary prevention, additional agent(s) will be required. We suggest here that the combination with ambroxol hydrochloride may result in synergistic benefit.

5. Ambroxol in GD and PD patients

In GD the misfolded and dysfunctional GCase proteins are retained in the ER instead of being trafficked to the Golgi apparatus and the lysosomes [9]. The resulting accumulation, attempted refolding and disposal of the protein leads to ER stress via the unfolded protein response, contributes to cellular dysfunction and programmed cell death [45,46]. Ambroxol hydrochloride, a mucolytic agent that potentiates the activity of sodium channels, has been shown to act also as a pharmacological chaperone [47]. As such, it facilitates proper folding of proteins in the ER and their trafficking to the final location within the cellular membrane or destination organelle.

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