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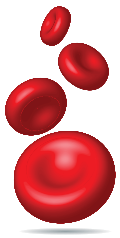
Gaucher disease and comorbidities: B-cell malignancy and parkinsonism



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Data emerging from the International Collaborative Gaucher Group (ICGG) Gaucher Registry together with other contemporary clinical surveys have revealed a close association between Gaucher disease and non-Hodgkin's B-cell lymphoma and myeloma and Gaucher disease and Parkinson's disease. Several possible explanations for increased B-cell proliferation and neoplasia in Gaucher disease have been proposed, including the possible influence of sphingosine (derived from the extra lysosomal metabolism of glucosylceramide), gene modifiers, splenectomy and immune system deregulation induced by cytokines, chemokines, and hydrolases released from Gaucher cells. Parkinson's disease is frequently seen in the otherwise-healthy relatives of Gaucher disease patients leading to the finding that *GBA* mutations represent a genetic risk factor for Parkinson's disease. The mechanism of the association between *GBA* mutations and Parkinson's disease has yet to be elucidated but the pathogenesis appears distinct from that of Gaucher disease. Several pathogenic pathways have been proposed including lysosomal and/or mitochondrial dysfunction. The effect of Gaucher disease specific therapies on the incidence of cancer or Parkinson's disease are not clear and will likely be evaluated in future ICGG Gaucher Registry studies.
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Introduction

The inception of the International Collaborative Gaucher Group (ICGG) Gaucher Registry (clinicaltrials.gov NCT00358943) made a brilliant virtue out of a commercial necessity. This requirement as part of the approval conditions to accompany the introduction of the first commercial therapy for Gaucher disease has led to an unprecedented series of publications and a burgeoning increase in knowledge and confidence in our knowledge of this disease.

In a very rare disorder with diverse manifestations, clinical understanding becomes ever fractured as arcane disease-related phenomena emerge. How do we define comorbidities, as opposed to unusual sequelae? For these purposes, they are defined as those disorders associated with Gaucher disease in a manner that we do not understand, conditions related to the underlying condition by common association, but where the mechanistic link is not understood. Some patients with Gaucher disease develop pulmonary infiltrates and while we cannot explain this heterogeneity, inspection of the lung tissue is likely to reveal predictable pathological features; but not so in the case of non-Hodgkin's B-cell lymphoma and myeloma, and with Parkinson's Disease–true comorbidities linked by close association with Gaucher disease as confirmed by emerging ICGG Gaucher Registry and other contemporary clinical surveys.

Gaucher Disease and B-Cell Neoplasia

For many years the association of Gaucher disease and polyclonal gammopathy as well as monoclonal gammopathy of undetermined significance has been reported [1,2]. In addition, there have been numerous reports showing an increase in certain neoplasms such as multiple myeloma, hepatocellular carcinoma, and B-cell non-Hodgkin's lymphoma (NHL) [3–5]. The cause of the increased frequency of these cancers is unclear, but here we elaborate on B-cell immunoproliferation and B-cell neoplasms associated with Gaucher disease and some of the theories advanced to explain their origin. These associations have been more sharply defined by utilizing data obtained from the ICGG Gaucher Registry.

Polyclonal gammopathy without any other underlying disease except for Gaucher disease has been noted in a number of studies, and monoclonal gammopathy of undetermined significance has been reported at an increased prevalence of 8–35% in patients with Gaucher disease and at younger ages [1,2] when compared with the general population [6]. The relative risk of developing multiple myeloma was 5.9 in a study from the ICGG Gaucher Registry [3] and was very similar to that reported in another study from Israel [4]. In one further study, the standardized rate ratio of

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developing multiple myeloma, calculated as the ratio of observed cases in the Gaucher disease cohort to expected numbers from the Dutch population, was 51.1 in the 131 patients included in the analysis [5]. The course of myeloma and outcomes were not described in any of these studies. Non-Hodgkin's lymphoma of good, intermediate, and poor prognostic types has also been noted to have an increased incidence in Gaucher disease [7–9]. Again, the clinical course of these patients with this cancer is not described in the literature, but anecdotally, in the experience of one of the authors (BR), the course and response to treatment did not differ from that observed in patients without Gaucher disease.

Despite the reported increased incidence of B-cell proliferation and neoplasms in patients with Gaucher disease, little is known about causation, although several explanatory theories have been put forward. For example, as a result of deficiency of acid β-glucosidase (glucocerebrosidase), glucosylceramide accumulates in the lysosomes of macrophages and after deacylation, its water-soluble derivative, glucosylsphingosine, can diffuse into the cytosol [10]. One of the byproducts of β-glucosylsphingosine, sphingosine, can build up as a result and is considered by some to have carcinogenic properties [11]. Although this appears to be an attractive hypothesis, the topic is clearly controversial, as reported in a recent review article [12]. For example, the idea that therapies used in Gaucher disease might induce certain cancers in these patients has been advanced. However, this seems highly implausible since there is no evidence that cancer in Gaucher disease was less frequent before the advent of therapy; indeed, in relation to the most commonly associated malignancy, multiple myeloma, this has been found to be a common cause of death in the era before enzyme therapy was introduced. In fact, there are studies suggesting that the prevalence has remained stable, if not decreased, and that most cancer-afflicted Gaucher patients with the N370S genotype were diagnosed with cancer before treatment for Gaucher disease was started [12].

Accumulation of glucosylceramide in macrophages gives rise to so-called Gaucher cells, which are in effect alternatively activated macrophages that release proinflammatory and anti-inflammatory cytokines, chemokines, and hydrolases [13]. It has been shown that the cytokines IL-6 and CCL-18 are released and it has been suggested that these molecules serve to promote gammopathies. Interleukin-6 has long been implicated as a signal transduction agent in multiple myeloma [14]. The transition from polyclonal gammopathy to monoclonal gammopathy of undetermined significance and then to multiple myeloma, as a result of clonal expansion, has been proposed to be a plausible continuum [15]. In this context, an extensive study recently reported by Nair et al. [16] shows that the pathological sphingolipids overproduced in Gaucher patients are recognized by a rare subset of CD1d-restricted human and murine type II natural killer T cells of the T-follicular helper phenotype. Such cells, obtained from mice with inducible Gaucher disease and also patients with the condition, were able to provide efficient cognate help to B-cells in vitro. In vivo, the lipids increased sphingolipid-specific type II NKT cells and as a consequence, downstream induction of germinal center B-cells, hypergammaglobulinemia, and antisphingolipid antibodies. This elegant study provides strong evidence of a direct link between the specific biochemical abnormality and B-cell proliferation, and in all likelihood contributes to cytokine-induced "alternative" macrophage activation (M2 phenotype) adopted by the eponymous Gaucher cell.

Another attractive hypothesis involves immune dysregulation in Gaucher disease because of enhanced release of cytokines by the alternatively activated macrophage leading to chronic B-cell stimulation [13]. For instance, the plasma concentration of interleukin-6 has been reported to be elevated in plasma from patients with Gaucher disease, and has been suggested as a candidate cytokine for the high incidence of polyclonal gammopathy, monoclonal gammopathy of undetermined significance, and multiple myeloma [14].

Gene modifiers have been raised as possible initiating agents in the causation of neoplasia. For instance, the incidence of multiple myeloma may be higher in those with the N370S genotype [8]. Patients who are homozygous for the mutant N370S GBA1 allele tend to have milder disease and live longer [17], and it has been suggested that the acid β-glucosidase folding mutation in N370S homozygotes may render them more susceptible to monoclonal gammopathy of undetermined significance and myeloma [18,19]. However, as yet, no long-standing studies are available to determine whether patients with Gaucher disease and any particular *GBA1* genotype are preferentially at risk for the development of neoplasia.

In one report, patients with Gaucher disease who had undergone splenectomy were suggested to be at greater risk of developing a malignancy [20] although this possible link was questioned in a later study [21]. Nevertheless, in the inducible strain of Gbatm1Karl/tm1KarlTg(Mx1-cre)1Cgn/0 mice that mimic human Gaucher disease, clonal expansion of B-cells is very striking, and there was a relatively high frequency of large B-cell tumors and myeloma accompanied by the presence of polyclonal gammopathy and appearance, in some animals, of monoclonal paraprotein(s) in serum ("M-spike"); the influence of splenectomy has yet to be determined in this model [22]. Since the advent of enzyme augmentation therapy in recent years, splenectomy is rarely carried out in patients with Gaucher disease and any contribution of this procedure to the risk of malignancy is likely to be reduced [23]. Of note, experimental administration of the potent inhibitor of UDP-glucosylceramide transferase, eliglustat (now approved for clinical use as Cerdelga®, Genzyme, a Sanofi company, Cambridge, MA), has recently been reported to prevent the emergence of paraproteinaemia and B-cell tumors in this mouse strain. As predicted, exposure to eliglustat greatly reduced Gaucher-related tissue β-glucosylceramide and plasma β-glucosylsphingosine concentrations; tissue lymphoproliferation in mice without manifest tumors was found to be significantly diminished in those animals with Gaucher disease that had been exposed to the drug [24].

It is clear that patients with Gaucher disease have an increased incidence of B-cell proliferation and neoplasia. Despite the emergence of theories advanced to explain these observations, the cause remains unknown. Clearly several avenues for future investigation of this important clinical association are possible; but the recent description of B-cell lymphomas and plasmacytomas that secrete monoclonal immunoglobulins that arise with a high frequency in an inducible murine model of Gaucher disease type 1 provides a living testing ground for experimental studies suggested by comorbid clinical association [22].

Gaucher Disease and Parkinson's Disease

The neurological manifestations of Gaucher disease are additional comorbidities not directly related to organ infiltration. The former clinical categories of Gaucher disease types 2 and 3 are defined by their neurological sequelae [25]. Gaucher disease type 1 was always considered to be nonneuronopathic, but there is an increased incidence of parkinsonism [26], and an alleged peripheral neuropathy in type 1 patients [27].

Parkinson's disease is a common, progressive neurodegenerative disorder that typically presents at about 70 years of age with a movement disorder comprising bradykinesia, rigidity, resting tremor, and postural instability as well as a range of nonmotor neurological impairments. Parkinsonism is also seen in a number of other rarer conditions including Gaucher disease type 1 where it is now known that at postmortem, patients with Gaucher disease and parkinsonism have several of the neuropathological features of Parkinson's disease, including alpha-synuclein-positive Lewy bodies in the cortex and brainstem [28]. In addition, Parkinson's disease is frequently seen in

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the otherwise-healthy relatives of Gaucher disease patients [29], which led to the hypothesis that *GBA* mutations might constitute a genetic risk factor for Parkinson's disease.

This has now been established in cases of both familial [30] and sporadic Parkinson's disease with a recent, international, multicenter collaborative study identifying one of two specific *GBA* mutations in 3% of over 5000 Parkinson's disease patients with an odds ratio for any *GBA* mutation of 5.43 for cases versus controls [31] although the risk is dependent on the nature of the *GBA* mutation [32]. This figure is in line with that found in a UK-based study [33]. *GBA1* mutations are also seen in significant numbers of patients with dementia with Lewy bodies but not multiple system atrophy, other disorders characterized by alpha synuclein aggregation [34,35]. Not only does the *GBA* mutation link to developing Parkinson's disease but it also appears to contribute to clinical heterogeneity in that compared with idiopathic Parkinson's disease; patients carrying *GBA1* mutations (GBA^{MUT}-PD) have an earlier age at onset, more symmetrical clinical signs, and an increased incidence of neuropsychiatric disturbance [28]. Clinical features that agree with imaging data showing that patients with GBA^{MUT}-PD have a more severe pathology at any given time [36,37].

In our own (RB) epidemiological longitudinal study of newly diagnosed incident cases of Parkinson's disease, about 10% of patients with sporadic Parkinson's disease had a known heterozygote mutation within the *GBA* gene or a polymorphism that may be pathogenic [38]. In this study the patients did not have an earlier onset of Parkinson's disease compared with GBA^{MUT}-PD individuals but did have a more aggressive form of the illness with an early dementia and more profound gait impairment, factors known greatly to impair quality of life.

These studies therefore confirm that the *GBA1* mutation (whether homozygous or heterozygous) not only increases susceptibility for Parkinson's disease, but also drives the disease process. As such, understanding how this occurs mechanistically may give insights into the pathogenesis of Parkinson's disease at a broader level.

The mechanism of the association between *GBA1* mutations and Parkinson's disease is yet to be elucidated but the pathogenesis appears distinct from that of Gaucher disease, where deficiency of acid β-glucosidase leads to accumulation of substrate, primarily in cells of the macrophage system. In GBA^{MUT}-PD it has been proposed that the *GBA1* mutations may act by a gain of function in which the protein misfolds and by so doing either increases the propensity for alpha synuclein to aggregate or reduces its clearance possibly through an alteration in lysosomal function and autophagy. An alternative hypothesis is that the mutation affects enzymatic activity, which then leads to problems of substrate clearance and lysosomal function.

To date the evidence suggests that the mutant acid β-glucosidase leads to a significant decrease in protein level and enzyme activity in several sites in the brain and spinal cord, most notably the substantia nigra [39]. This loss of activity interferes with normal autophagic processes enhancing the aggregation of alpha-synuclein [40], with which it has been shown to co-localize in Lewy bodies in vitro [41]. This may then be aggravated through a process that is self-perpetuating whereby the loss of acid β-glucosidase creates a positive feedback loop of reduced lysosomal function, which leads to α-synuclein accumulation, which in turn further inhibits lysosomal acid β-glucosidase function [42]. It has recently been shown that there are reduced glucosylceramidase protein and enzyme activity levels in fibroblasts from individuals carrying the *GBA1* mutation—in individuals with Parkinson's disease, without Parkinson's disease, and with Gaucher disease. This activity can be restored by ambroxol hydrochloride, which has led to a clinical trial of this agent in patients with Parkinson's disease harboring mutations in the *GBA1* gene [43]. This mechanism of pathogenesis is attractive, but not all studies support this [44] and other pathogenic pathways have been proposed.

While lysosomal dysfunction may lie at the heart of the pathogenesis of GBA^{MUT}-PD, it may also relate to mitochondrial dysfunction, either directly [45] or indirectly, and consequently impaired autophagy [46]. In this respect, the accumulation of ceramide as a result of deficient acid β-glucosidase activity has been shown to influence the methylation status of PGC1-alpha, a transcription factor recently identified to have a major influence upon mitochondrial bioenergetics and risk for Parkinson's disease [47,48].

Finally, it has been proposed that *GBA* mutations may interfere with the degradation of misfolded proteins by the endoplasmic reticulum. Endoplasmic reticulum-associated degradation typically involves the polyubiquination of proteins allowing them to be directed to the proteasome and degraded. A link between dysfunctional endoplasmic reticulum-associated degradation and Parkinson's disease is supported by the observation that mutations in the gene encoding parkin, a ubiquitin ligase, cause a Mendelian form of Parkinson's disease [8] and that mutant acid β-glucosidase acts as a substrate for parkin-mediated endoplasmic reticulum-associated degradation [49]. In addition, it has recently been shown that *GBA* mutation carriers retain acid β-glucosidase isoforms in the endoplasmic reticulum and have a reduced unfolded protein response, which may exacerbate the direct lysosomal defects described in this condition [50]. In sum, the findings emphasize that these degradation pathways do not function in isolation but interact at various levels.

In summary, *GBA* mutations are the single most frequent genetic risk factor for Parkinson's disease and are not only implicated in its genesis but also in its clinical course and phenotypic expression. How the various genetic defects in *GBA* cause the Lewy body pathology characteristic of Parkinson's disease at the cellular level is not fully understood, nor why only some patients with these mutations develop this neurodegenerative condition.

Conclusions

B-cell neoplasia (including multiple myeloma) and Parkinson's disease are divergent but true comorbidities of Gaucher disease. While the relationship between Gaucher disease and myeloma has been consolidated by the research occasioned by the ICGG Gaucher Registry, Parkinson's disease is now a matter of recent and intense fascination for which the future work of Registry should be adapted. As ably demonstrated here, both associations are of arresting scientific interest, but they are also a source of burgeoning concern for a community of patients who might feel that frontline biopharmaceutical enterprise has with one hand given them hope and renewed quality of life, only to have the fateful fingers of the other point to dark clouds in the near-distance.

If there were a comfort, it is this: like other very rare inborn errors of metabolism, Gaucher disease is a paradigm case with numerous features that are generally applicable for clinical understanding in important conditions that are widespread in all populations [51]. All now see that those loyal to the study of Gaucher disease have opened a small domain to the vast landscape of therapeutic science where, sooner or later, its haunting legacies will be embraced by the healing art.

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