LETTER TO THE EDITOR

Reply: Lysosomal dysfunction in Parkinson’s disease

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Sir,

McNeill highlights in his Letter to the Editor that glucocerebrosidase (GBA) gene mutation carriers have reduced glucosylceramidase protein and enzyme activity based on measurements obtained from patient fibroblasts (McNeill et al., 2014). He links this to our data recently presented in Murphy et al. (2014) identifying similar findings in brain regions associated with increased \(\alpha\)-synuclein early in Parkinson’s disease without GBA mutations, and suggests that reduced glucosylceramidase protein and enzyme activity plays a key early and not a secondary role in Parkinson’s disease. Although our data fully concur with this concept, we have been cautious to suggest an absolute direct link, i.e. reduced glucosylceramidase leads to increased \(\alpha\)-synuclein, which leads to Parkinson’s disease, based on evidence that most carriers of GBA mutations (both with Gaucher disease and heterozygotes) do not develop Parkinson’s disease (Rana et al., 2013; Alcalay et al., 2014). Current data show that only 1–5% of patients with GBA mutations will have Parkinson’s disease by the age of 60–65 years, with this proportion rising to around 10% by age 80–85 years (Rana et al., 2013; Alcalay et al., 2014). This data shows that GBA mutations that decrease glucosylceramidase protein and enzyme activity significantly increase the risk of Parkinson’s disease, but also that many people with GBA mutations will survive without ever getting Parkinson’s disease. It will therefore be important to identify the cellular factors that modify the risk of Parkinson’s disease, and particularly the dopamine cell loss, in GBA mutation carriers.

In addition, a similar small proportion of patients with Parkinson’s disease have GBA mutations (Sidransky and Lopez, 2012). Although the marked dopamine cell loss associated with Parkinson’s disease is not a feature of Gaucher disease, our data show that most patients with Parkinson’s disease do have reduced glucosylceramidase, even without GBA mutations, and that this occurs before \(\alpha\)-synuclein deposition in Lewy pathologies but when cellular \(\alpha\)-synuclein is increasing (Murphy et al., 2014). Thus we would concur with McNeill that either and/or both of these changes should be targeted for therapeutic intervention. We also show that a variety of other lysosomal changes occur at this time (Murphy et al., 2014), and as pointed out by McNeill, this is consistent with a number of diverse studies using patient fibroblasts and measurements from CSF. Importantly, the magnitude of the changes observed in different patient groups (Parkinson’s disease with and without GBA mutations and Gaucher disease) was similar, supporting the concept that lysosomal dysfunction is important in Parkinson’s disease as well as in Gaucher disease, and that for a proportion of cases with Parkinson’s disease, the mechanism for such dysfunction includes a GBA mutation and for the remainder of cases the mechanism is unclear. Based on these observations, it is likely that factors more common in Parkinson’s disease influence the changes observed and these now need to be identified.

It would seem that the lysosomal dysfunction in Parkinson’s disease and Gaucher disease may produce different lipid profiles (Abbott et al., 2014; Ferraz et al., 2014), even with similar small brain increases in glucosylceramide without accumulation. This further suggests additional important modifying factors differentiate these diseases. Our work in Parkinson’s disease shows a reduction in ceramide levels (Abbott et al., 2014; Murphy et al., 2014), whereas ceramide levels are not reduced in either neuropathic Gaucher disease or its animal model (Farfel-Becker et al., 2014; Ferraz et al., 2014). Increased GBA2 activity is thought to compensate and maintain ceramide levels in Gaucher disease (Ferraz et al., 2014), whereas we have shown that there is down-regulation of \(de novo\) ceramide synthesis in Parkinson’s disease in addition to its reduction through reduced glucosylceramidase activity (Abbott et al., 2014). As many functions of

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α-synuclein occur in association with lipid membranes, and the α-synuclein in Lewy bodies deposits around a central core of lipid (Gai et al., 2000), further work detailing important lipid changes in Parkinson’s disease may provide further clues into the pathogenic pathways affecting brain dysfunction in Gaucher disease versus Parkinson’s disease.

While we agree with much of the sentiment of the letter by McNeill, particularly the case made for the early therapeutic targeting of glucosylceramidase in patients with Parkinson’s disease, we also have some reservations based on the observations above and that Gaucher disease is not Parkinson’s disease. It may be that alternate mechanisms also impair lipid and lysosomal pathways in Parkinson’s disease, with further experiments warranted to fully describe the cellular phenotype associated with increased cellular α-synuclein in the brains of patients with Parkinson’s disease.

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**References**


