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No evidence that glucosylsphingosine is a biomarker for Parkinson disease: Statistical differences do not necessarily indicate biological significance

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To the editor:

We read with great interest the recent paper by Surface *et al* entitled "Plasma glucosylsphingosine in subjects with *GBA1* mutations with and without Parkinson's disease"(1). While the data presented, which suggested slightly higher levels of glucosylsphingosine in *GBA1* mutation carriers, may well be valid, we were quite surprised by the authors' conclusion that plasma glucosylsphingosine may serve as a useful biomarker for *GBA1*-related Parkinson disease (PD). Throughout the article, there are several assertions that do not support this interpretation.

Starting with the Abstract, statements made in the Results and Conclusions sections directly contradict each other. First it is stated that "Plasma glucosylsphingosine was significantly higher in N370S heterozygotes compared to non-carriers, *independent of disease status*." Yet the Conclusion suggests that their findings "…open up its future assessment as a *clinically meaningful biomarker* of *GBA1*-PD." In addition, in the paper's concluding sentence, the authors speculate whether glucosylsphingosine might be associated with PD risk or progression. Since glucosylsphingosine levels did not correlate with PD status, even in cases that already meet clinical diagnostic criteria, how can this be a biomarker for *GBA1*-related PD?

When following patients with Gaucher disease, glucosylsphingosine levels are indeed a useful biomarker correlating with disease severity and treatment efficacy(2,3). However, glucosylsphingosine levels in patients with Gaucher disease are often orders of magnitude higher than in controls. In contrast, the levels of plasma glucosylsphingosine in N370S heterozygotes reported here are uniformly below 1.4 ng/ml (mean 0.73–0.82ng/ml) (Figure 1a), and would still be considered in the normal range for healthy individuals. Moreover, there is clear overlap between levels in their controls and *GBA1* heterozygotes, with or without PD. Thus, the "statistically significant" differences observed between subjects

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with and without the N370S variant, are not likely biologically significant or clinically meaningful.

While we do appreciate that this is a brief report, several other limitations of the study were not discussed. The presented data did not address potential fluctuations in glucosylsphingosine levels that may occur in a given individual. Our experience is that when patients are followed longitudinally, fluctuations in glucosylsphingosine levels are observed over time both in carriers and patients with Gaucher disease, regardless of treatment status. In addition, the authors do not address whether plasma levels of the biomarker reflect what is occurring in the central nervous system (CNS). In fact, currently, evidence regarding whether the lipid accumulates in brain tissue or cerebrospinal fluid in PD remains unresolved (4).

Thus, we fear that while description of the cohort and data may be solid, the interpretation and conclusions derived from thse results are actually misleading. The data included does not show that glucosylsphingosine levels are a relevant biomarker reflecting the development of PD in subjects carrying the N370S *GBA1* variant. The slightly higher levels observed remain in the normal range and there is no scientific evidence provided suggesting that such small group differences are indeed physiologically or clinically relevant.

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