The Importance of Correct Phenotyping in Gaucher Disease

Keywords: Gaucher disease; phenotyping
DOI: 10.1177/0883073807305783

Recently, it has been claimed that patients with Gaucher disease type 1 have subclinical neurological signs as indicated by electrophysiological measurements.1 These findings, if substantiated, are very significant in the management of Gaucher disease.

In type 1 disease (nonneuronopathic), enzyme replacement therapy is the therapy of choice, with substantial biomedical correction achieved in most patients. In neuronopathic disease, efficacy of enzyme replacement therapy is doubtful in controlling neurological manifestations of the disease,2,4 and current consensus is that larger doses are required for type 3 patients.5 Clinical trials for an alternative treatment are under way.6

Clearly, any finding of neurological abnormalities in type 1 disease similar to those seen in type 3 disease will be a great consternation for many families and physicians. We are, however, concerned by the published data in this study. Two important issues need to be carefully clarified before these results can be accepted: (1) the questionable diagnosis of type 1 disease in this study and (2) the interpretation of their auditory brainstem response and other electrophysiological data.

Phenotype Identification

A crucial assumption in the Perretti et al1 study is that all their patients indeed had type 1 disease. The distinction between type 1 and type 3 disease is made on the absence or presence of abnormal saccadic eye movements (called saccade initiation failure, horizontal supranuclear gaze palsy, or ocular motor apraxia). As we have previously shown, it is easy to miss abnormal eye movements based on purely clinical observation.7 False negatives often occur because children and adults with type 3 disease do not always exhibit the typical head thrusting that has become popularly associated with saccade initiation failure. It is crucial to examine the saccadic eye movements directly by manual spinning8 or preferably by saccade initiation failure. It is crucial to examine the saccadic head thrusting that has become popularly associated with adults with type 3 disease do not always exhibit the typical

Auditory Brainstem Response Data

The auditory brainstem response (ABR) is a standard electrophysiological technique for assessing auditory brainstem integrity. We have previously shown that measurements of eye movements and audiological function are reliable subclinical and presymptomatic tests of neurological involvement in Gaucher disease.2,4 The waveform presented in their Figure 2 is from a L444P homozygote and is typically expected in type 3 disease showing prolonged I-III interval and poor morphology. In the absence of definitive eye movement recording, we cannot accept these data as evidence of neurological involvement in type 1 disease.

In addition, because the ABR can be distorted by both central (brainstem) and peripheral disorders, it is important to establish the degree of hearing, as well as any ABR abnormalities. A conductive hearing loss could explain the delayed I-V latency in some of the reported cases. Further audiometric studies, including pure tone audiometry, stapedial reflexes, and tympanometry, would be needed to clarify the origins of these abnormalities.

The question of abnormal electrophysiological findings is usually based on the standard deviation of inlaboratory control data. It seems that the authors have made independent decisions on each individual test in each individual. This is highly questionable as it will almost certainly lead to false-positive claims.

In conclusion, without objective phenotyping with eye movement recording and standard multivariate statistical comparison to a control group, the data presented by Perretti et al1 cannot be taken as evidence for significant abnormalities in type 1 disease.

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References


