

Outcome Measures for the New Treatments of Lysosomal Storage Diseases – The Neuronopathic Gaucher Disease Experience

a report by

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Lysosomal storage disorders (LSDs) represent a group of over 45 distinct hereditary metabolic diseases (HMDs) that affect children and adults. With a combined prevalence of one in 5,000 births, this is a major public health problem placing an enormous burden on the individuals and affected families. Following the successful introduction of enzyme replacement therapy (ERT) for Gaucher disease (GD) a decade ago, a new era of realistic treatments for LSDs and other HMDs is dawning. New treatments for Fabry's disease and mucopolysaccharidosis (MPS) 1, and trial developments for GD type 3, Niemann-Pick type C (NPC) and B (NPB), G_{M2} gangliosidosis, infantile and late-onset Pompe and MPS 2, 4, 6 and 7 are currently under way. Consequently, there is now an unprecedented demand for early diagnosis and longitudinal monitoring of disease status in these conditions.

Many LSDs are associated with neurodegeneration, often with an onset in early childhood or infancy. New potential drug therapies must halt – or, ideally, reverse – the neurological disease as early as possible. However, the development of quantitative neurological outcome measures for monitoring patients and clinical trials has not kept pace with progress in molecular medicine. The ability to test the neurological efficacy of new therapies is very limited, if not absent, for the young or cognitively impaired child – it is imperative that this issue is addressed as soon as possible.

In this article, the authors review their recent experience in quantitative neurological assessment of neuronopathic (n)GD. The authors have shown that measurements of eye movements and audiological function have provided a reliable subclinical and pre-symptomatic test of neurological involvement. These measurements have not only provided reliable early diagnosis, but are also being used as primary neurological biomarkers ('neuromarkers') in current clinical trials for nGD and NPC disease. Oculomotor and audiological functions are also compromised early in other HMDs (especially the LSDs), although systematic investigations are scant. The authors propose that

these techniques have, potentially, a wide application in baseline assessment and longitudinal monitoring of patients in trials or on treatment for many HMDs.

An Overview of GD

GD is an autosomal recessive HMD with a genetic locus on chromosome 1q21–31. It is the most common LSD with an incidence of one per 57,000 live births caused by a deficiency in the enzyme glucocerebrosidase, which is important in the recycling of membrane lipids. The deficiency leads to accumulation of the substrate glucocerebroside (glucosylceramide or ceramide β -glucoside) in macrophages (Gaucher cells) in the spleen, liver, bone, lungs and brain. Typical systemic signs include hepatomegaly, hypersplenism, thrombocytopenia, anaemia and bone disease, but there are marked variations in disease severity. Primary neurological signs occur in approximately 10% of the population (depending on ethnicity) and include eye movement abnormalities, audiological dysfunction, myoclonus, electroencephalogram (EEG) abnormalities and bulbar palsy.

Historically, GD has been divided into three types:

- type 1 – non-neuronopathic (without primary neurological involvement);
- type 2 – acute infantile neuronopathic (severe neuronopathic disease leading to death by the third year); and
- type 3 – subacute neuronopathic (with less severe and more variable neurological involvement).

There are more than 150 known Gaucher mutations. However, the relationship between genotype and phenotype is surprisingly discordant. Some genotype–phenotype correlations are clinically useful. For example, a single copy of the N370S mutation appears to be neuro-protective. Homozygotes for the L444P or D409H mutations are almost always associated with neuronopathic disease. However, the diagnosis of neuronopathic

disease is currently based largely on clinical examination. Due to the insidious nature of the neurological progression, it can be difficult to diagnose nGD in the young child until irreversible overt signs appear.

The introduction of ERT (Cerezyme®) has placed an imperative on the early distinction between type 1 and type 3 disease to allow the appropriate treatment to commence as soon as possible. In most patients, ERT can lead to substantial systemic biochemical correction with increased longevity and quality of life. However, in type 2 infants with severe neurological disease, ERT has not prevented fatal neurological progression, even though systemic disease has been responsive. In type 3 disease, the neurological response to ERT is less certain, and for those patients, most centres recommend much higher doses than for non-neuronopathic patients.

A more recent therapeutic development is substrate depletion using N-butyldeoxynojirimycin (OGT918 or Zavesca®). Recent clinical trials of Zavesca have shown significant amelioration of hepatosplenomegaly and haematological manifestations in type 1 GD patients, but it is still not known whether it can reverse the neurological deficits in nGD.

Both Cerezyme and Zavesca are expensive therapies with annual costs often cited at US\$150,000 for Cerezyme (for 60u/kg/2wk), while Zavesca is estimated to cost more than US\$115,000. The extreme cost precludes high-dose treatment for all GD patients, making it essential to identify the phenotype as early as possible, before overt and irreversible neurological signs occur.

Eye Movement Abnormalities

A range of eye movement abnormalities have been described in nGD. The authors focus on the most common abnormalities, which are saccade initiation failure (SIF) and slowing of saccadic eye movements. These are diagnostic of neuronopathic disease in a patient already diagnosed with GD.

SIF

The triggering abnormality has been labelled variously as 'ocular motor apraxia', 'supranuclear gaze palsy', 'looping' or 'SIF'. Here, the term SIF will be used.

Horizontal (h-)SIF is a defect in the triggering of horizontal saccades, making it difficult for the patient to make horizontal shifts of gaze with the eyes. Young children may spontaneously develop compensatory strategies to shift gaze, such as hypermetric head thrusts or synkinetic blinking in which the child is able to initiate a saccade by a blink.

However, reliance on compensatory behaviours as diagnostic signs leads to false negatives. Instead, SIF can be reliably detected by triggering saccades directly. In children, this is most easily done by inducing optokinetic nystagmus (OKN) or vestibular nystagmus (VN) and examining the timing of quick-phases, which are reflexive saccades. This can be carried out on patients of any age (including the neonatal period) and provides a reliable diagnostic tool for neuronopathic disease.

Neuronopathic patients often exhibit vertical (v-)SIF. This probably occurs later than h-SIF, but there have been no systematic studies. Children with downward (d-)SIF often exhibit downward head thrusts, but upward (u-)SIF is often accompanied by blinking.

Although SIF can be detected at any age and has considerable diagnostic value when properly assessed, it is difficult to use as a longitudinal quantitative measure. The authors are currently exploring this problem, but saccade slowing is more suited for monitoring purposes.

Saccade Slowing

Most (if not all) nGD patients will also exhibit slow horizontal saccades (when they can be generated) and many will often have slow downward and less often upward saccades. This can be very difficult to detect by simple clinical observation, but by using specialised eye movement recording, it is possible to measure saccade speed from school-age children. The authors have also been able to measure saccade speed in healthy infants, but further methodological development is needed before this can be applied to very young children with HMDs. The advantage of measuring saccade speed is that it provides a quantitative measure of eye movement performance.

Pathophysiology

The pathophysiology of SIF *per se* is unclear, as it can be associated with a wide range of underlying disorders, often involving the basal ganglia, cerebellum, brainstem or reflecting general white matter disease. v-SIF has been associated with mid-brain disorders. The presence of slow horizontal and vertical saccades strongly implicates disseminated abnormalities in the supranuclear brainstem saccade circuits for horizontal saccades (the paramedian pontine reticular formation) and vertical saccades (rostral mid-brain). ■

This article is continued, with references, tables and a graphic, in the Reference Section on the website supporting this business briefing (www.touchbriefings.com).