Prospects for Treatment of the Neuronopathic Form of Gaucher Disease

a report by

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Introduction to Gaucher Disease

Gaucher disease (GD) results from the defective activity of the lysosomal enzyme acid ß-glucocerebrosidase. Continued accumulation of undegraded substrate results in multi-organ pathology affecting the spleen, liver, lungs, bone marrow and bone. In neuronopathic forms the brain is also affected, whereas in the non-neuronopathic form the residual activity of ß-glucocerebrosidase is sufficient to degrade glucocerebroside in the central nervous system (CNS). The disease is progressive and disease dynamics may vary throughout life.

Clinically, the neuronopathic GD (NGD) variants acute neuronopathic (type 2) and chronic neuronopathic (type 3) variant present a remarkable spectrum of phenotypes ranging from the neonatal lethal form to a slowly progressive disease type. These variants are rare, affecting less than one in 100,000 individuals.[1]

Genotype/phenotype correlations are imperfect, although the presence of at least one N370S allele appears to preclude the development of neuronopathic involvement. Homozygosity for the L444P genotype is almost always associated with the chronic neuronopathic form and the D409H/D409H genotype results in a rare neuronopathic phenotype with aortic valve calcification.

Neuropathology/Pathogenesis

The pathological mechanism of CNS damage in the neurological forms of GD is still not fully understood.[3–5] The neuronopathological features of the neuropathic forms consist of infiltration of the Virchov–Robin space with Gaucher cells (lipid-laden macrophages). It is possible that toxic or metabolic factors extrinsic to neurons induce neuronal dysfunction in these patients. Neuronal loss and neurodegeneration with damaged neurons have been reported in the basal ganglia, nuclei of the midbrain, pons and medulla, cerebellum, dentate nucleus and hypothalamus. Gray matter and white matter gliosis and neuronal storage of glucosylceramide have been reported. It has been shown that neurons harmed by the disease process were more sensitive to glutamate-induced neuronal cytotoxicity and to toxicity induced via various other cytotoxic agents.[6]

Clinical Features of Neuronopathic Gaucher Disease

Neuronopathic Gaucher disease (NGD) can be defined as the presence of neurological symptoms in a patient who has a confirmed diagnosis of GD. In addition, there should be no other explanation for the neurological symptoms. Although NGD is considered to represent as a wide spectrum of heterogeneous clinical phenotypes, the historical disease classifications are too well-known to be ignored and, in fact, are still very useful for clinicians. Traditionally, NGD is divided into the lethal neonatal forms (acute NGD variants) without evidence of pyramidal tract involvement (type 2a) and with marked evidence of this symptom (type 2b). Chronic NGD includes the type 3a variant which has severe, pronounced neurological symptoms and relatively mild visceral involvement. Type 3b patients have fewer expressed neurological manifestations and perhaps supranuclear saccadic gaze palsy as the only neurological symptom. Usually, these type 3b patients demonstrate marked enlargement of the liver and in particular of the spleen and bone deformities;[4] this phenotype includes the Norrbottnian variant. In addition, there is also a type 3c variant that, in addition to its neurological component, is also characterised by aortic valve calcification.[7]

The most characteristic and consistent feature of all chronic NGD is an abnormality of horizontal gaze, which more precisely should be referred to as supranuclear saccadic gaze palsy. It can be the only neurological sign at presentation and, in some patients, can remain unnoticed for some period of time leading to initial inaccurate diagnosis of non-NGD (type 1).[8] Older children can compensate for their poor saccades by a combination of synkinetic blinking and head thrusting. Patients with type 3a and some with type 3b NGD develop a progressive encephalopathy characterised by multi-focal myoclonic movements

resistant to medical therapy. These myoclonic movements are usually of neocortical origin, proving a general cortical pathogenic process that occurs in all NGD patients, but with varied intensity and time of onset. Among the many atypical neurological features that have been observed, the most important are extrapyramidal involvement leading to characteristic rigidity in childhood and to a Parkinson-like presentation in older patients.[9] NGD patients show auditory dysfunction.[10] Intellectual development in type 3 patients is within normal limits or patients may be mildly retarded. In practice, this permits fully normal social functioning of this group of patients.

Therapeutic Options

In the past, many patients underwent splenectomy that initially resulted in haematological improvement. Subsequently, skeletal deformities worsened dramatically, usually in the form of kyphosis of the thoracic spine and chest deformities with protrusion of the sternum. In addition, splenectomised patients with type 3b NGD tended to develop severe neurological symptoms in subsequent years.

Patients with severe and rapidly progressing NGD have, in the past, received bone marrow transplants.[11] Although stabilisation of neurological involvement has been achieved, the associated high morbidity and mortality rates preclude recom-mendation of bone marrow transplantation in the current management of NGD.[12] Longer term follow-up of these transplanted Norrbottnian patients may indicate that neuronopathic damage still occurs, albeit delayed by one, or several, decades.

Enzyme Replacement Therapy

The introduction of enzyme replacement therapy (ERT) for GD patients was an indisputable milestone in the treatment of metabolic diseases, not only because treating the cause of the disease became a reality, but mainly because of its unquestionable success. Over the years it became increasingly clear that therapeutic management of GD patients with Cerezyme® (imiglucerase, Genzyme Corporation) should be individualised given the remarkable diversity in clinical presentation and disease progression and the inter-patient variability in treatment responses of organ compartments. In October 2003, an international panel of physicians with extensive expertise, with the clinical management of Gaucher patients, met. The purpose of their meeting was to reach consensus on evidence-based, therapeutic goals for Cerezyme treatment with reference to each organ system affected in non-neuronopathic GD (thus excluding the neurological compartment). Analyses on data from the Gaucher Registry database (more than 3,000 patients worldwide), as well as the collective experiences of the panel, were used to generate goals addressing the key manifestations of non-neuronopathic GD. For details please refer to the publications by Pastores et al.[13] and Weinreb et al.,[14] which provide practical disease management tools. The therapeutic goals, as defined for each individual disease compartment, are to be achieved within the expected timeframes and maintained throughout the patient's life, rendering on-going monitoring of the patient's condition vital for effective management. Given the changeable disease dynamics, it is necessary to individually tailor the Cerezyme dosages.

The key conclusion arising from the accumulated experiences is that ERT should be started as early as possible after diagnosis. The most-used starting dose of Cerezyme is 60U/kg body weight per bi-weekly intravenous (IV) infusion, followed by periodic evaluation of achievement/maintenance of the therapeutic goals and, if warranted, cautious dose adjustments.

For the paediatric (non-neuronopathic GD) population, guidelines were recently published – for diagnosis and clinical assessments,[15] as well as for treatment and outcome monitoring.[16,17] These guidelines aim at early intervention to alleviate the disease burden and prevent irreversible damage from occurring. High-dose treatment should be started in children as soon as the diagnosis is ascertained and continued at least until growth parameters, i.e. height and weight, have normalised.

The spectacular responses to ERT were a strong incentive to consider initiation of Cerezyme in neuronopathic patients; despite the theoretical problem of intravenous ERT is not likely to pass the blood–brain barrier. In the case of acute NGD (type 2) patients, the ineffectiveness of ERT on the CNS was soon demonstrated. Even high doses of Cerezyme cannot halt neurological progression of the disease as was recently reiterated by Campbell et al.[18] ERT was first administered to chronic NGD (type 3) patients in 1995. For some Swedish patients with the Norrbottnian variant of NGD, delayed progression of neurologic disease was reported but, in general, the results were not encouraging.[19] Since then, despite Cerezyme only initially being recommended for non-neuronopathic GD, many centres worldwide have been treating chronic NGD patients with ERT. There are no unequivocal results pointing to ERT as an effective treatment of neurological symptoms, which, as also previously outlined, show enormous heterogeneity across the NGD spectrum.[19] Published observations, however, as well as anecdotal reports, suggest that Cerezyme may sometimes ameliorate non-myoclonic manifestations of chronic NGD 3.[12]

These data should be interpreted with caution, as in NGD the neurological deficit cannot be properly determined and the net effect of ERT on the most common neurological manifestations is difficult to ascertain. In one study, cerebrospinal fluid analysis showed a significant increase in glucocerebrosidase levels in cerebrospinal fluid after ERT dosages of 120U/kg per month.[20]

In order to provide guidance with regard to the controversial issue of ERT in NGD patients, the European Working Group on GD has issued treatment guidelines.[12] ERT is recommended to be initiated as soon as possible after diagnosis for patients with chronic NGD, siblings of patients with NGD with a confirmed diagnosis and patients with the L444P/L444P, D409H/D409H, or L444P/ D409H genotype. ERT should be commenced at a starting dose of 120U/kg per two weeks and doubling the dose to 240U/kg per two weeks should be considered if neurological involvement progresses. If, despite dosage increase, neurological involvement progresses and renders quality of life unacceptable, the dose of Cerezyme should be reduced to a level that controls the systemic manifestations of GD. All patients at risk of NGD, without evidence of neurological involvement, should receive Cerezyme at a minimum dose of 60U/kg per two weeks.

Recommended assessments of neurological involvement in GD include neurological examination performed by a neurologist, eye movement examination (electro-oculography and ophthalmoscopy), measurement of peripheral hearing (electro-acoustical), brain imaging (magnetic resonance imaging (MRI) or computed tomography (CT)), neurophysiology (electroencephalogram (EEG) and brain stem evoked response (BSER)) and neuropsychometry (intelligence quotient (IQ)).[12]

There is no doubt that ERT is effective at ameliorating the visceral manifestations of chronic NGD (type 3). ERT, however, should be started at a high dose in these patients as soon as the diagnosis is confirmed, in order to prevent irreversible severe skeletal deformities. Children with chronic NGD need higher doses and longer treatment to reach normal height and weight, compared with children with non-NGD ('type 1') (author's personal observation).

In 2003, the The European Agency for the Evaluation of Medicinal Products (EMEA) issued a positive opinion on expanding the indications for Cerezyme to include chronic NGD and subsequently the European marketing authorisation for this product was expanded to include chronic NGD.

Uncovering and describing the natural history of NGD and the effects of ERT is still at an early stage. The broad spectrum of phenotypes associated with NGD, as well as differences in phenotypic expression within various ethnic populations complicate the discussions concerning prognosis and the potential benefits of therapy. It is, therefore, crucial to collect more clinical data for NGD patients from different countries.

Substrate reduction therapy (SRT) is a new form of treatment that aims to reduce the delivery of potential substrate material to the macrophage system. Recently, substrate inhibition therapy with miglustat (Zavesca®) was approved for treatment of symptomatic patients with mild to moderate non-neuronopathic GD for whom ERT is unsuitable.[21] Substrate reduction therapy represents a potentially new treatment for the neurological symptoms in chronic NGD, although it still has to be proven that such treatment can actually reach the affected brain areas and have a clinical effect. Although the current indications for use of Cerezyme and Zavesca[21,22] precludes combination therapy, a combination of Cerezyme and a brain-targeted SRT may become a therapeutic modality in the future, once newer-generation SRT agents may have been tested and have been shown to be more specific and less toxic.

The full description of the natural history of non-neuronopathic and neuronopathic GD remains very important. International Registry programmes (databases) are helpful in expanding the scope of knowledge about the broad phenotypic spectrum of rare diseases such as GD and other lysosomal storage diseases, e.g., Fabry disease, Pompe disease and Mucopolysaccharidosis 1 (MSP-1). These registries will provide further guidance for optimal therapeutic management of these diseases. ■

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