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ORIGINAL ARTICLE

Management of neuronopathic Gaucher disease: Revised recommendations

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Summary The original guidelines drawn up for the management of the neuronopathic forms of Gaucher disease were felt to be in need of revision; in particular, the role of high-dose enzyme replacement therapy (120 IU/kg of body weight every 2 weeks) in stabilizing neurological disease. The existing published evidence was analysed; it was concluded that it did not support the role of high-dose ERT, although this might be required to treat severe visceral disease.

Abbreviations

ERT	enzyme replacement therapy
EWGGD	European Working Group on Gaucher Disease
NGD	neuronopathic Gaucher disease

Introduction

'Neuronopathic' forms are the rarest variants of Gaucher disease (GD), with an estimated incidence of <1 in 100 000 live births (Beutler and Grabowski 2001). The neuronopathic forms, like other GD variants, are pan-ethnic, although a particularly high prevalence of neurological involvement has been documented among patients with GD in Northern Sweden (Erikson 1986), in Poland (Tylki-Szymanska et al 2006) and in the Jenin Arab population (Abrahamov et al 1995).

The management of neuronopathic Gaucher disease (NGD) is fraught with difficulty. In particular, the role of enzyme replacement therapy (ERT) is unclear. In

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2001, the European Working Group on Gaucher Disease (EWGGD) appointed a Task Force on Neuronopathic Gaucher Disease to make recommendations for the management of NGD. These were duly completed and published; the challenges faced have been described earlier (Vellodi et al 2001).

It was felt that the time had come to review data from Europe and elsewhere and, if appropriate, make revised recommendations. A literature search found three studies since 2001 on the effect of ERT on neurological progression. Specifically, the benefit of high-dose enzyme replacement therapy on neurological progression was looked for. It is generally accepted that 'high-dose' refers to doses of 120 units/kg or higher every 2 weeks.

In a study of 32 patients, Goker-Alpan and colleagues found no effect of ERT on neurological progression. However, only two patients had received 120 units/kg per 2 weeks (Goker-Alpan et al 2008). Erikson and colleagues reported the outcome of eight Norbottnian patients on ERT (Erikson et al 2006). None of them had been receiving high-dose ERT.

Davies and colleagues reported follow up of 55 European patients. The majority of the patients were homozygous for the L444P mutation. All had been on enzyme replacement therapy (ERT). However, there was considerable variation in the dose of ERT, as well as an uneven distribution of risk factors. Thus, the oldest patients were on the lowest doses, and several had had a total splenectomy, while the youngest patients had a high proportion of compound heterozygosity and were on the highest doses, and very few had had a splenectomy. This heterogeneity rendered analysis very difficult. However, some observations were possible. The older patients appeared to remain relatively stable despite a conventional dose of ERT (60 units/kg per 2 weeks). In general older/adult patients have mild disease; this might be an explanation of this 'stable' status (Tylki-Szymanska and Czartoryska 1999). In the younger patients, there was no clear effect of high-dose ERT on neurological outcome. However, the period of follow-up was too short in many patients to allow valid conclusions to be drawn (Davies et al 2007a).

Based on the available data, the conclusion of this group was that there was no evidence that high-dose ERT prevented or slowed down neurological progression in these patients. Accordingly, the recommendations regarding ERT dose need to be revised. However, it was felt that this was a good opportunity also to review and, if necessary, revise the other recommendations for management.

We would like to stress that these recommendations only refer to the neurological aspects of NGD. Management of other aspects of Gaucher disease is comprehensively described elsewhere (Maas et al 2008; Pastores et al 2004).

The revised recommendations of the Task Force will be discussed under the following headings:

1. Definition
2. Classification
3. Monitoring
4. Treatment
5. Patient/Family Counselling and Role of Patient/Family Organizations

1. Definition

Neuronopathic Gaucher disease (NGD) can be defined as the presence of neurological involvement in a patient with biochemically proven GD, for which there is no explanation other than GD.

2. Classification

Any classification should address the current unwieldy proliferation of subcategories of NGD. We propose that the terms 'type 2' and 'type 3' GD be dropped, as they fail to take account of the spectrum of NGD phenotypes. Instead, the terms, 'acute' and 'chronic' NGD should be used.

Acute NGD

This refers to the onset at $\leq$1 year of age of progressive bulbar involvement (stridor, squint, swallowing difficulty). Pyramidal involvement (opisthotonus, head retroflexion, spasticity, trismus) and cognitive impairment may or may not be present. The earlier classification into two groups (Vellodi et al 2001) should be dropped.

Chronic NGD

This refers to all patients with NGD who do not have acute NGD. We consider further subdivision of this group (e.g., into types A, B, etc.) to be artificial, as its clinical spectrum is too heterogeneous. Types IIIA and IIIB simply represent two clinical groups. Furthermore, while the D409H homozygotes undoubtedly represent a distinct clinical subgroup (Abrahamov et al 1995), it is highly probable that more new variants will be described. The current classification is not flexible enough to accommodate them.

An intermediate form of NGD has been described. This is characterized by a relatively late age of onset but eventually rapidly progressive neurological disease (Goker-Alpan et al 2003). In the early stages these patients may be erroneously labelled as having type III GD.

3. Monitoring

A full initial neurological assessment should be performed in the following groups:

A. All newly diagnosed GD patients.
B. Particular attention should be paid to any patient with GD who has one or more of the following risk factors for development of NGD:

- Sibling of a patient with proven NGD.
- 'High-risk' genotypes, including L444P/L444P, D409H/D409H or L444P/D409H. Genotyping should be confirmed by direct sequencing of DNA, particularly in cases where L444P alleles are suspected. Restriction fragment length polymorphism (RFLP) testing is unable to distinguish the L444P allele, with its T→C translocation, from the L444R allele, with its T→G translocation (Uchiyama et al 1994). Unlike the L444P allele, the L444R allele is not associated with neuronopathic disease. Furthermore, only by sequencing will the complex recombinant alleles that include L444P be detected.
- Onset of severe systemic GD at ≤2 years of age

Subsequent neurological monitoring should be carried out regularly in all the above groups, *whether or not neurological involvement is detected initially*, as it may be detected later.

Tables 1 and 2 presents the Task Force's revised recommended protocols for initial neurological assessment (Table 1) and subsequent neurological monitoring (Table 2). These represent the minimum clinical protocols that attempt to utilize generally available, cost-effective technology, while at the same time yielding the greatest possible amount of clinically relevant data. From past experience, consistent and meaningful assessments across the board are required in order to effectively monitor these patients.

4. Treatment

Table 3 presents the Task Force's recommended treatment guidelines for NGD. These were made against the following background of evidence:

- In both non-neuronopathic and neuronopathic GD, ERT has demonstrated an excellent safety profile.
- There is clear evidence in most patients that ERT ameliorates systemic involvement (skeletal deterioration, visceromegaly, haematological abnormalities) in non-neuronopathic as well as chronic NGD, enhancing quality of life.
- There is no evidence that ERT has reversed, stabilized or slowed the progression of neurological involvement.

Table 1 Minimum clinical protocol for initial assessment of primary neurological involvement in GD

1. Clinical examination
- Neurological examination, preferably by a neurologist with experience in neuronopathic GD.
- Eye movement examination, preferably by a neuro-ophthalmologist or a neurologist. At the minimum, elicitation of repeated maximal amplitude horizontal saccades should be performed at the bedside and compared with a healthy subject. It is desirable to add an objective measurement, e.g. DC electro-oculography, as clinical examination alone often misses slowed saccades or gaze palsy (Harris et al 1999).
- Additional neuro-ophthalmological investigation, including direct ophthalmoscopy.
- Measurement of peripheral hearing (electro-acoustical emission in small children, pure tone audiometry in older patients).

2. Brain imaging
- Preferably by magnetic resonance imaging (MRI), or, if MRI is unavailable, by computed tomography (CT). In very sick children, the risks of anaesthesia should be considered, and the scan deferred until the child is clinically stable.

3. Neurophysiology
- Electroencephalography (EEG).

4. Neuropsychometry
- Age-appropriate testing should be assessed by an appropriately qualified psychologist. It may be advisable to defer testing, especially in young children, until the patient's overall health is sufficiently improved to permit meaningful measurement. Widely available protocols, such as the Wechsler Intelligence Scale for Children® - Fourth UK Edition (WISC-IVUK), should be used unless not valid for language or cultural reasons. Specific testing, e.g. of speech and language, memory, visuospatial skills, etc may be required. Such testing should be tailored to the needs of the individual child.

Table 2 Minimum clinical protocol for neurological follow-up in GD

1. Clinical examination
- Neurological examination: every 3 months during year 1, every 6 months thereafter. Neurological examination to include scoring as defined in the Severity Scoring Tool for NGD (Davies et al 2007b) to monitor changes. In adolescent and adult patients who are stable, neurological examination once a year may be sufficient.
- If eye movements were considered to be normal at the time of initial assessment or if the result was equivocal (often the case with very young or sick children), such testing should be repeated.
- Additional neuro-ophthalmological investigation: only if clinically indicated, e.g. development of sixth-nerve palsy.
- Peripheral hearing (audiometry or electro-acoustical emissions depending on age, as stated above): evaluating trends every 2 or 3 years.

2. Brain imaging
- Only if clinically indicated. The risk of anaesthesia should be considered. An exception to this may be made in patients who have the D409H allele. Such patients may be at risk of hydrocephalus (Inui et al 2001; Shiihara et al 2000), and may therefore need to be scanned on a regular basis.

3. Neurophysiology
- EEG: only if clinically indicated, e.g. by presence of seizures. If myoclonus is suspected, telemetry may be needed.
- Nerve conduction velocity: only if clinically indicated with reported symptoms of tingling, numbness, pins and needles.

4. Neuropsychometry
- Annual assessments are probably not necessary as they are time-consuming. We suggest the following: assessment at school entry, then at transition from primary to secondary school, then when transitioning to college/adult education. Age-appropriate scales should be used.

- In patients with established acute NGD, ERT has had little effect on the progressively downhill course. It has merely resulted in prolongation of pain and suffering (Bove et al 1995; Elstein et al 1998; Erikson et al 1993; Prows et al 1997).
- There is evidence (Erikson 1986; Kyllerman et al 1990) that in chronic NGD, total splenectomy is associated with increased severity and rate of progression of neurological and bone involvement (Erikson 1986) and/or risk of infection, and possibly, with diminished response to ERT (Czartoryska et al 2000). Total splenectomy should therefore be avoided as far as possible. However, it may occasionally be necessary in order to improve response to therapy (Krasnewich et al 1998). In this situation we would recommend a partial rather than a total splenectomy (Altarescu et al 2001).

Table 3 Recommended treatment guidelines

- Currently, enzyme replacement therapy (ERT) with macrophage-targeted recombinant human glucocerebrosidase (Cerezyme, Genzyme Corporation, Cambridge, MA, USA) is the treatment of choice.
- In children with chronic neuronopathic Gaucher disease (NGD), as soon as possible after diagnosis, ERT should be commenced in a starting dose of 60 U/kg of body weight every 2 weeks.
- The dose may need to be increased from time to time to control visceral disease, e.g. increase in hepatosplenomegaly, exacerbation of pulmonary disease, or unexplained systemic symptoms such as malaise or irritability accompanied by a significant deterioration in biomarkers such as chitotriosidase activity. However, it should not be allowed to fall below 60 units/kg per 2 weeks.
- In adults, a dose of 30–60 units/kg per 2 weeks should suffice, as visceral stability was demonstrated at this dose.
- ERT cannot be recommended for patients with acute NGD. The management of these children should be along the lines of managing severe, rapidly progressive neurological disease in infancy and early childhood. In addition, problems specific to brainstem involvement, such as severe laryngospasm, swallowing and respiratory problems, must be managed appropriately. We accept that this is an important area, However, a detailed description is beyond the scope of this article. In the 'intermediate' form (Goker-Alpan et al 2003) a trial of treatment may be warranted if it is not clear immediately that there is rapidly progressive neurological disease. However, as soon as this becomes evident, treatment should be withdrawn.
- The management of the adult patient is also critical. Such patients tend to have not only significant visceral disease but also the problems that are associated with chronic, progressive neurodisability in adults. However, this discussion, while important, is again beyond the scope of this article.
- Splenectomy is contraindicated in all but emergency situations, for example splenic rupture or profound thrombocytopenia necessitating platelet transfusions or life-threatening internal haemorrhage. In such instances, partial, rather than total, splenectomy should be considered. All such patients should be treated as if they had had a total splenectomy, i.e. pneumococcal immunization, prophylactic penicillin. A splenectomy of a large but functionally destroyed spleen is indicated in a rare patient whose systemic disease does not respond to high dose ERT and when all other causes of resistance to ERT have been excluded.

5. Counselling and the role of patient/family organizations

Professional counselling can improve quality of life for families of patients at high risk for or with established NGD, as well as facilitate informed case management decision-making. Such counselling should, therefore, be recommended to and made available for all such families. In addition, counselling for decision making for 'end-of-life issues' as well as bereavement counselling should be provided to parents and siblings of infants with acute NGD.

Patient/family organizations can be an extremely valuable source of support and information for families, and newly diagnosed patients should be given contact information for their national or local organizations. The Task Force wishes to emphasize the desirability of the closest possible cooperation between treating physicians and patient/family organizations. On an ongoing basis, these two groups can and should provide each other with feedback and support in optimizing management of NGD.

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