J. Inherit. Metab. Dis. 24 (2001) 319–327

Management of neuronopathic Gaucher disease: A European consensus

NEURONOPATHIC GAUCHER DISEASE TASK FORCE OF THE EUROPEAN WORKING GROUP ON GAUCHER DISEASE:
A. VELLODI[1]*, B. BEMBI[2], T. B. DE VILLEMEUR[3], T. COLLIN-HISTED[4], A. ERIKSON[5], E. MENGEL[6], A. ROLFS[7] and A. TYLKI-SZYMANSKA[8]
[1] *Metabolic Unit, Great Ormond Street Hospital for Children, London, UK;* [2] *Pediatric Clinic, Instituto per la Enfanza 'Burlo Garofalo', Trieste, Italy;* [3] *Neuropaediatric Service, Hôpital Trousseau, Paris, France;* [4] *Gaucher's Association of the United Kingdom, London, UK;* [5] *Department of Paediatrics, Umeå University, Umeå, Sweden;* [6] *Children's Hospital, University of Mainz, Mainz, Germany;* [7] *Neurology Clinic, University of Rostock, Rostock, Germany;* [8] *Child Health Institute, Warsaw, Poland*

* *Correspondence: Metabolic Unit, Great Ormond Street Hospital for Children NHS Trust, Great Ormond Street, WC1N 3JH, London, UK. E-mail: Ashok.Vellodi@gosh-tr.nthames.nhs.uk*

MS received 20.07.00 Accepted 6.08.00

'Neuronopathic' forms (Erikson et al 1997; Patterson et al 1993) are the rarest variants of Gaucher disease, with an estimated incidence of <1 in 100,000 live births (Beutler and Grabowski 1995). The neuronopathic forms, like other Gaucher disease variants, are pan-ethnic, although a particularly high prevalence of neurological involvement has been documented among patients in Northern Sweden (Erikson 1986) in Poland (Tylki-Szymanska et al 1996) and in the Jenin Arab population (Abrahamov et al 1995).

The management of neuronopathic Gaucher disease is fraught with difficulty. There is a lack of standard assessment protocols, and this, together with treating physicians' varying access to technology and degree of experience, has resulted in wide variations in clinical practice. This is reflected in reported results. The role of enzyme replacement therapy in the treatment of neuronopathic Gaucher disease is therefore still far from clear.

The European Working Group on Gaucher disease in 1999 appointed a Task Force on Neuronopathic Gaucher Disease to analyse both published and unpublished recent data and, on the basis of this analysis, to present their recommendations.

The Task Force faced the following challenges in evaluating and formulating strategies for management of neuronopathic Gaucher disease.

1. While untreated neuronopathic Gaucher disease tends to be progressive, the rate of progression is extremely variable and is difficult if not impossible to predict. In the Norbottnian cohort of patients with chronic neuronopathic disease, for example, the neurological course of untreated patients was found to worsen slowly but, even in this genetically homogeneous group, to vary considerably between patients (Erikson 1986).
2. Some patients progress only very slowly, if at all (Ida et al 1999). The impact of treatment in such patients may therefore take years to manifest itself.
3. The variable rate of progression of untreated neurological involvement, together with the rarity of neuronopathic Gaucher disease, renders prospective clinical studies impractical.

The group recognized that there are many unanswered questions, and any recommendations will have to be subjected to rigorous review at regular intervals as fresh evidence becomes available. However, in the absence of any randomized controlled trials, a consensus-based approach was felt to be a suitable starting point. However, the group was able to draw on experience with over 70 patients from its members' centres or the world literature. The results and recommendations of the review are presented in this report. It is hoped that this will serve as a resource enabling health professionals, patients and families to optimize care for individuals with neuronopathic Gaucher disease. The management of the severe lethal neonatal variant is not discussed, as it is not generally considered to be a neuronopathic form of Gaucher disease. Similarly, Parkinson disease is not discussed.

The 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.

DEFINITION

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

CLASSIFICATION

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

Acute neuronopathic Gaucher disease: This refers to the onset at $\leqslant$ 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. Two subgroups can be identified: (A) little or no evidence of pyramidal tract involvement, irritability or cognitive impairment; (B) marked evidence of pyramidal tract involvement, irritability and cognitive impairment. Pyramidal involvement invariably is associated with cognitive impairment, and is a poor prognostic sign.

Chronic neuronopathic Gaucher disease: This refers to all patients with Gaucher disease who do not have the acute form. 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.

MONITORING

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

A. All Gaucher disease patients with neurological signs or symptoms.
B. Any patient with Gaucher disease who has one or more of the following risk factors for development of neuronopathic Gaucher disease:

- Sibling of a patient with proven neuronopathic Gaucher disease.
- '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 Gaucher disease at $\leqslant$ 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.

Table 1 presents the Task Force's recommended protocols for initial neurological assessment and subsequent neurological monitoring. These represent 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.

Table 1 Minimum clinical protocols

Initial assessment of neurological involvement in Gaucher disease

1. *Clinical examination*
   - Neurological examination performed by a neurologist, preferably one with experience in neuronopathic Gaucher disease.
   - Eye movement examination, preferably by an ophthalmologist and preferably with objective measurement, e.g. DC electro-oculography, since 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).
3. *Neurophysiology*
   - Electroencephalography (EEG).
   - Diagnostic brain stem evoked responses (BSER).
4. *Neuropsychometry*
   - Intelligence quotient (IQ) should be assessed, but it may be advisable to defer testing, especially in young children, until the patient's overall health is sufficiently improved to permit meaningful measurement. Whenever possible, widely available protocols, such as the WISC-III, should be used.

Follow-up of neurological involvement in Gaucher disease

1. *Clinical examination*
   - Neurological examination: every 3 months during year 1, every 6 months thereafter.
   - Eye movement examination: every 6 months.
   - Additional neuro-ophthalmological investigation: every 12 months.
   - Peripheral hearing: every 12 months; results should be evaluated in terms of 2- or 3- year trends.
2. *Brain imaging*
   - Only if clinically indicated.
3. *Neurophysiology*
   - EEG: only if clinically indicated, e.g. by presence of seizures.
   - Threshold BSER: every 12 months.
4. *Neuropsychometry*
   - Every 12 months.

TREATMENT

Table 2 presents the Task Force's recommended treatment guidelines. They were made against the following background of evidence.

In both non-neuronopathic and neuronopathic Gaucher disease, enzyme replacement therapy (ERT) has demonstrated an excellent safety profile.

Table 2 Recommended treatment guidelines

1. Currently, enzyme replacement therapy (ERT) with macrophage-targeted recombinant human glucocerebrosidase (Cerezyme®, Genzyme Corporation, Cambridge, MA, USA) is the treatment of choice.
2. The following groups should receive treatment:
   - Patients with chronic neuronopathic Gaucher disease.
   - Siblings of patients with neuronopathic Gaucher disease who are proven to have Gaucher disease.
   - Patients with the L444P/L444P, D409H/D409H or L444P/D409H genotype.
3. As soon as possible after diagnosis or identification, ERT should be commenced in a starting dose of 120 U/kg of body weight every 2 weeks until either
   - the patient has reached adulthood and clearly exhibits mild Gaucher disease and stable neurological involvement, at which point a reduced continuing dose *may* be considered, or
   - neurological involvement progresses. At this point, a short period (not more than 6 months) of doubling the dose to 240 U/kg every 2 weeks should be considered.
4. If, despite dosage increase, neurological involvement progresses so as to render quality of life unacceptable, the dose of ERT should be reduced to a level that controls the systemic manifestations of Gaucher disease.
5. All patients at risk of neuronopathic Gaucher disease, but with no evidence of neurological involvement, should receive ERT in a minimum dose of 60 U/kg every 2 weeks, and continue to be carefully monitored. The exception is siblings of known neuronopathic Gaucher disease patients, who should be treated as if they have the disease.
6. There is insufficient evidence to withhold treatment from children with acute neuronopathic Gaucher disease type A, i.e. with relatively unimpaired cognitive function. Such patients should be offered a 6-month trial of ERT, 120 U/kg every 2 weeks, with monthly follow-up at a specialist centre. However, at present, ERT cannot be recommended for patients with acute neuronopathic Gaucher disease type B.
7. Higher doses than those recommended may be needed to control visceral disease.
8. Splenectomy is contraindicated in all but emergency situations. 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.

There is clear evidence that ERT ameliorates systemic involvement in non-neuronopathic as well as neuronopathic Gaucher disease, enhancing quality of life.

There is preliminary evidence that ERT has reversed, stabilized or slowed the progression of neurological involvement in some patients.

- Among eight Swedish patients aged 4–42 years (mean 23 years) with chronic neuronopathic Gaucher disease, treated for 53–86 months, ataxia subjectively diminished in 3 of 4 with this symptom. Intelligence quotient (IQ) increased markedly—by one to three stanine steps—in 3 of 7 psycho-

metrically assessed patients. Epilepsy remained under control despite withdrawal of antiepileptic medication in one patient, and severe migraine headaches disappeared in another (Erikson, unpublished data). No neurological deterioration has occurred in any of the eight patients.

- After 18 months of ERT, ataxia also diminished in one German patient and IQ increased markedly in another. Both these individuals demonstrated a very clear improvement in acoustic evoked potentials mainly regarding amplitude and latency in waves III and IV (Rolfs, unpublished data).
- Of 10 children treated in the United Kingdom from 1.3 to 8.9 years, two showed neurological improvement. One child had considerable diminution of seizures without a change in his antiepileptic therapy. A second child has shown initial stabilization and then improvement of progressive ataxia and dystonic posturing (Vellodi et al 1999). The other eight children have remained stable.
- Presymptomatic ERT did not prevent development of acute neuronopathic Gaucher disease and death at age 15.2 months in an American infant. However, compared to a similarly affected older sibling, the presymptomatically treated child never developed upper motor neuron involvement and spasticity, had delays of 2–3 months in development of bulbar involvement and 5–6 months in development of squint and oculomotor paresis, and survived >6 months longer (Prows et al 1997).

In patients with established acute neuronopathic disease, 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, 1997; Prows et al 1997).

Preliminary evidence suggests that a dose of 120 U/kg intravenously every 2 weeks may be more effective than a dose of 60 U/kg every 2 weeks:

- The female pediatric patient with chronic neuronopathic Gaucher disease from the British series discussed above, who had had progressive ataxia and dystonic posturing on a dose of 60 U/kg every 2 weeks, improved on a dose of 120 U/kg every 2 weeks. In the same patient progressive cognitive deterioration (as shown objectively by WISC scores), has slowed since institution of the higher dose of ERT.
- The two German patients with chronic neuronopathic Gaucher disease discussed above, who showed neurological improvement, appear to have done so in the 24 months after their ERT dosage was increased from 60–80 U/kg every 2 weeks to 100–120 U/kg every 2 weeks (Rolfs, unpublished data).
- In a prospective statistical comparison among German and Swiss patients receiving ERT for chronic neuronopathic Gaucher disease, after a 2-year follow-up, a subgroup receiving ERT doses of 100–120 U/kg appeared to have achieved greater neurological improvement than a subgroup receiving lower doses (Rolfs, unpublished data). Neurological improvement was assessed by the Rostock Neuro Scoring system, a validated, semiquantitative scale that measures forms of Gaucher disease neurological

involvement that are clinical and least likely to be influenced by concomitant therapies, e.g. antiepileptic medications (Rolfs et al, manuscript in preparation). Systemic improvement was assessed by the Severity Score Index (Zimran et al 1989), the most widely applied semiquantitative scoring scale for systemic Gaucher disease.

- A prospective US National Institutes of Health (NIH) study (Schiffmann et al 1997) found that an intravenous infusion of 120 U/kg of macrophage-targeted glucocerebrosidase resulted in a significant increase in GCR activity in cerebrospinal fluid, while intravenous infusions of lower doses did not. This suggests that a dose of at least 120 U/kg may present the best chance of delivering enzyme to the central nervous system.

There is evidence (Erikson 1986; Kyllerman et al 1990) that in neuronopathic Gaucher disease complete or partial splenectomy is associated with increased severity and rate of progression of neurological and bone involvement and/or risk of infection, and possibly with diminished response to ERT (Czartoryska et al 2000).

Bone marrow transplantation (BMT) has been performed in six Swedish patients (Ringden et al 1995) and three British patients (Vellodi, unpublished data). With one exception, there was no deterioration in any of the patients, and at least one patient has shown reversal of neurological and neuroradiological abnormalities. There is thus evidence that BMT appears to be effective in the treatment of neurological progression in this disorder. However, there is significant attendant morbidity and mortality, and we do not therefore recommend BMT in the current management of neuronopathic Gaucher disease. It is possible, however, that in time the risk from BMT will diminish. We anticipate that our recommendations will be reviewed from time to time in the light of new developments. It is possible that developments in this area, together with an increased understanding of the factors predisposing to a poor outcome, will in time enable us to make appropriate recommendations.

PATIENT/FAMILY COUNSELLING AND ROLE OF PATIENT/FAMILY ORGANIZATIONS

Nondirective psychological counselling can improve quality of life for families of patients at high risk for or with established neuronopathic Gaucher disease, as well as facilitate informed case-management decision making. Such counselling should be recommended to and made available for all such families.

Patient/family organizations also 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 neuronopathic Gaucher disease.

A particularly difficult situation may arise in the case of an infant with acute type A disease who has been offered a trial of ERT for 6 months. The infant's condition may deteriorate rapidly, yet the parents may be reluctant for treatment to be withdrawn despite the most careful explanation beforehand. Such a situation will require sensitive handling. However, as the circumstances are likely to vary considerably from centre to centre, it is difficult to make firm recommendations as to how the situation should be handled.

REFERENCES

Abrahamov A, Elstein D, Gross-Tsur V, et al (1995) Gaucher's disease variant characterized by progressive calcification of heart valves and unique genotype, *Lancet* **346**: 1000–1003.

Beutler E, Grabowski GA (1995) Gaucher disease. In Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The Metabolic and Molecular Bases of Inherited Disease*, 7th edn. New York: McGraw-Hill, 2641–2670.

Bove KE, Daugherty C, Grabowski GA (1995) Pathological findings in Gaucher disease type 2 patients following enzyme therapy. *Hum Pathol* **26**: 1040–1045.

Czartoryska B, Tylki-Szymanska A, Lugowska A (2000) Changes in serum chitotriosidase activity with cessation of replacement therapy (cerebrosidase) administration in Gaucher disease. *Clin Biochem* **33**: 147–149.

Elstein D, Abrahamov A, Zimran A (1998) Ethical considerations for enzyme replacement therapy in neuronopathic Gaucher disease. *Clin Genet* **54**: 79–184.

Erikson A (1986) Gaucher disease—Norrbottnian type (III). Neuropaediatric and neurobiological aspects of clinical patterns and treatment. *Acta Paediatr Scand Suppl* **326**: 1–42.

Erikson A, Johansson K, Månsson J-E, Svennerholm L (1993) Enzyme replacement therapy of infantile Gaucher disease. *Neuropediatrics* **24**: 237–238.

Erikson A, Bembi B, Schiffmann R. (1997) Neuronopathic forms of Gaucher's disease *Ballière's Clin Hematol* **10**: 711–723.

Harris CM, Taylor DSI, Vellodi A (1999) Ocular motor abnormalities in Gaucher disease. *Neuropediatrics* **30**: 289–293.

Ida H, Rennert OM, Iwasawa K, Kobayashi M, Eto Y (1999) Clinical and genetic studies of Japanese homozygotes for the Gaucher disease L444P mutation. *Hum Genet* **105**: 120–126.

Kyllerman M, Conradi N, Månsson JE, Percy AK, Svennerholm L (1990) Rapidly progressive type III Gaucher disease: deterioration following partial splenectomy. *Acta Paediatr Scand* **79**: 448–453.

Patterson MC, Horowitz M, Abel RB, et al (1993) Isolated horizontal supranuclear gaze palsy as a marker of severe systemic involvement in Gaucher disease. *Neurology* **43**: 1993–1997.

Prows CA, Sanchez N, Daugherty C, Grabowski GA (1997) Gaucher disease: enzyme therapy in the acute neuronopathic variant. *Am J Med Genet* **71**: 16–21.

Ringden O, Groth CG, Erikson A, Granqvist S, Mansson JE, Sparrelid E (1995) Ten years' experience of bone marrow transplantation for Gaucher disease. *Transplantation* **59**: 864–870.

Schiffmann R, Heyes MP, Aerts JM, et al (1997) Prospective study of neurological responses to treatment with macrophage-targeted glucocerebrosidase in patients with type 3 Gaucher's disease. *Ann Neurol* **42**: 613–621.

Tylki-Szymanska A, Millat G, Maire I, Czartoryska B (1996) Types I and III Gaucher disease in Poland: incidence of the most common mutations and phenotypic manifestations. *Eur J Hum Genet* **4**: 334–337.

Uchiyama A, Tomatsu S, Kondo N, et al (1994) New Gaucher disease mutation in exon 10: a novel L444R mutation produces a new *Nci*I site the same as L444P. *Hum Mol Genet* 3: 1183–1189.

Vellodi A, Young E, Harris C (1999) The management of children with neuronopathic Gaucher disease; a single-centre experience. *Abstracts of the Third EWGGD Workshop, Lemnos*, p. 68.

Zimran A, Sorge J, Gross E, Kubitz M, West C, Beutler E (1989) Prediction of severity of Gaucher's disease by identification of mutations at DNA level. *Lancet* **2**: 349–352.

SOCIETY FOR THE STUDY OF INBORN ERRORS OF METABOLISM

The SSIEM was founded in 1963 by a small group in the North of England but now has more than 70% of its members outside the UK. The aim of the Society is to promote the exchange of ideas between professional workers in different disciplines who are interested in inherited metabolic disorders. This aim is pursued in scientific meetings and publications.

The Society holds an annual symposium concentrating on different topics each year with facilities for poster presentations. There is always a clinical aspect as well as a laboratory component. The meeting is organized so that there is ample time for informal discussion; this feature has allowed the formation of a network of contacts throughout the world. The international and multidisciplinary approach is also reflected in the *Journal of Inherited Metabolic Disease*.

If you are interested in joining the SSIEM then contact the Treasurer: Dr. J. R. Bonham, Department of Paediatric Chemical Pathology, Sheffield Childen's Hospital (NHS) Trust, Sheffield, S10 2TH, UK. The subscription includes the 8 issues of the *Journal of Inherited Metabolic Disease* as well as the regular circulation of a newsletter.

The SSIEM web site is on http://www.ssiem.org.uk