Eur J Pediatr (2004) 163: 67–75
DOI 10.1007/s00431-003-1363-z

ORIGINAL PAPER

04836

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Paediatric non-neuronopathic Gaucher disease: recommendations for treatment and monitoring

Received: 20 September 2003 / Accepted: 6 October 2003 / Published online: 16 December 2003
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Abstract In individuals with non-neuronopathic Gaucher disease, childhood manifestations are usually predictive of a more severe phenotype. Although children with Gaucher disease are at risk of irreversible disease complications, early intervention with an optimal dose of enzyme therapy can prevent the development of complications and ensure adequate, potentially normal, development through childhood and adolescence. Very few, if any, children diagnosed by signs and symptoms should go untreated. Evidence suggests that disease severity, disease progression and treatment response in different organs where glucocerebroside accumulates are often non-uniform in affected individuals. Therefore, serial monitoring of the affected compartments is important. This should include a thorough physical examination at 6- to 12-monthly intervals. Neurological assessment should be performed to rule out neurological involvement and should be undertaken periodically thereafter in children who are considered to have risk factors for developing neuronopathic disease. Haematological and biochemical markers, such as haemoglobin, platelet counts and chitotriosidase levels, should be assessed every 3 months initially, but when clinical goals have been met through treatment with enzyme therapy, the frequency can be reduced to every 12 to 24 months. Careful monitoring of bone disease is vitally important, as the resulting sequelae are associated with the greatest level of morbidity. By combining various imaging modalities, the skeletal complications of non-neuronopathic Gaucher disease can be effectively monitored so that irreversible skeletal pathology is avoided and pain due to bone involvement is diminished or eliminated. Monitoring must include regular psychosocial, functional status and quality-of-life evaluation, as well as consistent assessment of therapeutic goal attainment and necessary dosage adjustments based on the patient's progress. *Conclusion*: Through comprehensive and serial monitoring, ultimately, a therapeutic dose of enzyme therapy that achieves sustained benefits can be found for each child with non-neuronpathic Gaucher disease.

Keywords Gaucher disease · Management · Monitoring · Paediatric · Quality-of-life

Abbreviations *ACE* angiotensin-converting enzyme · *BMD* bone mineral density · *DXA* dual-energy X-ray absorptiometry · *QoL* quality-of-life · *TRAP* tartrate-resistant acid phosphatase

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Introduction

Enzyme therapy of paediatric Gaucher disease with glucocerebrosidase effectively ameliorates or reverses the visceral and haematological aspects of the disorder, with treatment responses observed within months [23]. Enzyme therapy can also prevent or reverse much of the skeletal pathology of Gaucher disease in children [2,23]. This has led to improved overall health and quality-of-life (QoL) for patients with the disease.

In November 2001, the authors of this paper (a group of international experts in Gaucher disease representing Germany, Israel, Italy, Spain, UK and USA) convened in Barcelona, Spain to discuss paediatric Gaucher disease, with a primary focus on the non-neuronopathic variant. Potential barriers contributing to the underrecognition of the burden of non-neuronopathic Gaucher disease in the paediatric population were identified and are discussed in an accompanying paper in this issue of the European Journal of Pediatrics [24]. These included the low awareness of the severity of disease in children, the paucity of data on the natural history of non-neuronopathic Gaucher disease in children and the unpredictability of its course from individual to individual. Since children have comprised only about 33% of patients enrolled in studies of enzyme therapy for Gaucher disease, there are fewer data on which to base optimal dosing regimens. Furthermore, the non-neuronopathic form of the disease has traditionally been referred to as "adult" Gaucher disease, although data from the Gaucher Registry show this to be a misnomer [13], as 66% of individuals with symptomatic non-neuronopathic Gaucher disease will manifest in the first two decades. As a result, optimal methods for monitoring disease progression in children have not been well defined. Similarly, there are no clear guidelines for the treatment of Gaucher disease in children; hence, further information is required on dosages, methods for assessing response to therapy and criteria for dosage adjustment.

In view of the above, we have formulated international recommendations on managing and monitoring children with non-neuronopathic Gaucher disease. These are based on the consensus of the group and will be the focus of this article.

Treatment goals

Non-neuronopathic Gaucher disease manifesting during childhood is usually indicative of a rapidly progressive course, associated with the development of irreversible, morbid complications [24]. Proper recognition of the specific nature of paediatric non-neuronopathic Gaucher disease and of a comprehensive evaluation of disease burden at presentation is essential [24]. Only then can opportunities and constraints for early preventative treatment of the most chronic and debilitating manifestations of non-neuronopathic disease in children be addressed. Therapy should aim to prevent irreversible pathology, normalise health and prevent the need for splenectomy, which is linked to an increased tendency for infections and a worsening of bone disease [3]. In addition, treatment should prevent bone crises and the subsequent fractures and alleviate the associated suffering. It should be recognised, however, that true "normality" may not be attainable in children with Gaucher disease, and that clinically relevant and achievable goals are represented by the reduction of signs and symptoms to a level that does not interfere with health and QoL.

Management of non-neuronopathic Gaucher disease in children

Psychosocial considerations

The roles of the physician, hospital, family and school are central to the management of Gaucher disease in young children, and the balance of roles between these different groups changes as the child progresses through adolescence and into early adulthood.

Enzyme therapy for paediatric non-neuronopathic Gaucher disease: efficacy in treating paediatric non-neuronopathic Gaucher disease

Early institution of enzyme therapy (imiglucerase; Cerezyme, Genzyme Corporation, Cambridge, MA, USA) can prevent the visceral and haematological complications of non-neuronopathic Gaucher disease. Institution of enzyme therapy after complications have arisen may result in their marked, but incomplete, amelioration. Enzyme therapy with alglucerase (Ceredase, Genzyme Corporation, Cambridge, MA, USA) and imiglucerase is efficacious for treating the visceral and haematological aspects of Gaucher disease, with treatment responses seen within months [23]. The goals for children receiving enzyme therapy should be:

1. Normalisation of haemoglobin levels
2. Improvement of platelet counts to safe levels (i.e. not associated with increased risk of haemorrhage)
3. Reduction of organ volumes to the point where they no longer produce symptoms [30]
4. Prevention of the need for splenectomy
5. Prevention of bone crises and subsequent fractures
6. Optimal growth

An analysis performed in 2001 of 196 children in the Gaucher Registry (age range 2.5 to 9 years) showed that growth, which had been suboptimal in more than 50%, improved following enzyme therapy [33]. It has been speculated that an improvement in insulin-like growth factor levels could be partly responsible for this [44]. Early treatment with enzyme therapy, therefore, prevents skeletal complications and although it may not increase the final height achieved, it does ensure that

growth is not delayed and prolonged, thus preventing considerable suffering during adolescence. A study by Kauli et al. [37] showed that enzyme therapy appears to normalise growth and possibly, the onset of puberty. Furthermore, a study by Kaplan et al. [32] showed that puberty was delayed in patients starting therapy in the middle of the second decade, but not in those starting therapy in the first decade.

A number of studies have shown that enzyme therapy with imiglucerase reverses bone marrow involvement and increases bone mineral density (BMD) in many paediatric patients [2, 23,45]. This suggests that enzyme therapy for paediatric patients may reduce the risk of serious skeletal complications such as pathological fractures and vertebral compression and may be an effective treatment for osteopenia [7]. In addition, enzyme therapy has been shown to reduce the frequency of bone crises in children with Gaucher disease [7] and to lessen the pain associated with bone crises and prevent subsequent fractures [17].

While haematological and visceral parameters improve within months, the response of the skeletal system is slower to occur and more difficult to measure. Evidence of skeletal improvement may require longer therapy and higher doses of enzyme therapy than are necessary to improve haematological and organ parameters. Indeed, improvements in BMD may take years, although children tend to respond better in this respect than adults [7,45]. This may be related to the faster metabolic rate of bone turnover in children [45].

Recommendations on dosing of enzyme therapy

Decisions on treatment with enzyme therapy should be made following diagnosis and a comprehensive burden-of-disease evaluation, as outlined by Grabowski et al. [24].

All symptomatic children with Gaucher disease should be treated. Although there are different views on the appropriate starting dose for adults, there is more of a consensus that children should receive higher doses. At least 30 U/kg every 2 weeks should be used, but many consider that 60 U/kg should be the minimum starting dose. Dose adjustments after initiation of enzyme therapy should be made on an individual basis, and may increase or decrease based on achievement of the therapeutic goals as assessed by regular monitoring of each patient's progress. As all patients should respond to enzyme therapy with an appropriate dose, the absence of an improvement in the visceral, haematological and biochemical markers within 6 months may indicate that a higher dose is required. If bone crises continue, the dose should be increased by at least 50% [17]. However, improvements in skeletal complications may take longer and may require higher doses. Diminished responses to therapy are noted with decreasing doses in adults, but such data have not been obtained in children. In addition, the rapid skeletal changes in children with growth indicate major differences compared to the remodelling that occurs in adults. This and the need to develop a competent skeleton suggest caution with dosage reduction in children. The dosage should not be reduced more frequently than every 6 months and it should not be reduced below 30 U/kg per 2 weeks. Finally, it is important to note that the actual dose must be adjusted periodically to account for the changing weight of the child.

Pain management

Analgesics are an important part of supportive therapy for patients with skeletal pathology associated with Gaucher disease. Infarctions, bone crises, fractures and osteonecrosis may be accompanied by severe and debilitating pain. Analgesic options include acetaminophen and non-steroidal anti-inflammatory drugs and, although narcotic analgesics have been cited as options for severe and limited events such as bone crises, they are not effective in all patients [16]. An alternative treatment is high-dose oral prednisolone, which has been reported to reduce periosteal oedema and provide relief of severe pain within hours – even pain refractive to morphine – during bone crises [16]. Concerns that high-dose steroids may cause bone disease (especially avascular necrosis) have been unsubstantiated [14,15], possibly because of the acute nature of the treatment. For severe cases of bone crises, hospitalisation may be required where intravenous hydration and pain control medications may be administered. If available, nuclear scans may help differentiate between osteomyelitis and bone crises.

Orthopaedic management

Orthopaedic surgical procedures are often needed to maintain function in patients with skeletal manifestations of Gaucher disease [8, 34, 36, 38, 42]. Pathological fractures may require surgical immobilisation and restoration. Osteonecrosis may necessitate joint replacement to restore mobility. The hips are the most common sites of joint replacement in patients with Gaucher disease, and patients who are candidates for knee arthroplasty have often already had hip replacement. Shoulder arthroplasty is also carried out as the proximal humerus can also develop osteonecrosis. Although in the past, patients as young as 17 years of age have benefited from total hip replacement, joint replacement in children should be carefully considered as it interferes with limb growth and prostheses have a relatively short lifespan.

Monitoring of non-neuronopathic Gaucher disease in children

Principles of monitoring

The same basic principles of monitoring should be applied to all children with non-neuronopathic

Gaucher disease, whether or not they are being treated with enzyme therapy. As outlined by Grabowski et al. [24], a full clinical examination should be performed at baseline in all patients to provide a reference point for consistent subsequent monitoring. The clinical needs of the individual patient, as defined by the goals set following an evaluation of disease burden at baseline, will influence the frequency of follow-up assessments and the techniques used to monitor patient progress, as will the availability of facilities. In some cases, more frequent evaluations than have been recommended here will be appropriate due to the severity of disease. In such cases, clinical judgment should be used to decide at what frequency tests should be performed.

Serial monitoring allows the rate of disease progression to be evaluated and can indicate whether clinical goals are being met in the expected timeframe. Repeat examinations are also required whenever a change in the dose of enzyme therapy is instituted. Table 1 summarises the recommended types and minimum frequencies of examinations.

Physical examination

After an initial physical examination at presentation, further physical examinations should be performed at 6- to 12-monthly intervals. Follow-up physical examinations should include evaluation of the skin, noting signs of bruising, petechiae, and pallor; the abdomen, to assess hepatic and splenic enlargement; growth (weight, height and head circumference); lung function and range of joint movement and gait.

Neurological monitoring

An essential criterion for the diagnosis of non-neuronopathic Gaucher disease is the absence of any CNS involvement. A diagnosis of neuronopathic disease can be ruled out at presentation based on objective eye movement and auditory assessments [5,25]. However, if access to these specialised tests and interpretation of their results by a trained individual is not possible, neurological monitoring should be carried out regularly

Table 1 Minimal recommendations for the monitoring of children with non-neuronopathic Gaucher disease (adapted from [12], with permission)

Assessment	Patients not receiving enzyme therapy		Patients receiving enzyme therapy			
	Every 12 months	Every 12–24 months	Not achieved therapeutic goals		Achieved therapeutic goals	At time of dose change or significant clinical complication
			Every 3 months	Every 12 months	Every 12–24 months	
Physical examination	Every 6 months			Every 6–12 months		X
Haematology						
Haemoglobin	X		X		X	X
Platelets	X		X		X	X
Biochemistry						
Chitotriosidase and/or TRAP and/or ACE	X		X		X	X
Visceral						
Spleen volume (MRI/ultrasound)		X		X	X	X
Liver volume (MRI/ultrasound)		X		X	X	X
Pulmonary function tests	X			X	X	
Cardiovascular function (echocardiography and ECG)	X			X	X	
Skeletal						
MRI (sagittal T1-weighted scan of spine; coronal T1-weighted scan of femora)		Routinely every 24 months		X	X	X
X-ray (chest, spine[a], pelvis and long bones)		X		X	X	X
DXA spine and hips		X		Every 12 months	Every 24 months	X
Other						
Pain	X			Every 6–12 months	X	X
QoL (using paediatric scoring system)	X			X	X	X

[a]Spinal X-rays films only when the patient is symptomatic (e.g. back pain), when disease is severe, there is poor growth or kyphosis

Table 2 Follow-up of neurological involvement in children with Gaucher disease (for details of baseline assessments, see [46]). Reproduced with kind permission of Kluwer Academic Publishers

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 to 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 brain stem-evoked responses: every 12 months
4. Neuropsychometry
   Every 12 months

[46] (Table 2), preferably by a paediatric neurologist, in children who do not have at least one N370S allele. It is recommended that clinical ocular motor testing follows the procedure of manual spinning as described by Cassidy et al. [11]. Regular monitoring of paediatric patients without an N370S allele, particularly children with a "high-risk" genotype and siblings of patients with proven neuronopathic Gaucher disease [46], is very important. It should also be noted that the distinction between severe non-neuronopathic disease and some forms of subacute neuronopathic disease is often not obvious in early childhood because neurological involvement in some patients may be insidious and may not manifest until late childhood or early adulthood [46]. Moreover, "non-typical" oculomotor and auditory abnormalities may occur occasionally as secondary phenomena of non-neuronopathic disease rather than primary neuronopathic manifestations.

Haematological markers

Anaemia and thrombocytopenia must be monitored regularly (Table 1) to ensure that haemoglobin levels and platelet counts are normalised. The standard haematological examination should include a full blood count and coagulation screening. Assessment of coagulation factor levels may also be appropriate; deficiency of factors IX and X is associated with Gaucher disease [12], and factor XI deficiency may coincide with Gaucher disease amongst the Ashkenazi Jewish population [8]. In addition, serum iron, iron-binding capacity and ferritin may be assessed, since haemosiderosis and hyper-ferritinaemia have been reported concurrently with Gaucher disease [12]. Finally, a marker predictive of disseminated intravascular coagulation, such as D-dimer, thrombin-antithrombin complex or acute-phase protein, may be measured, since elevated levels may indicate intrasplenic activation of the coagulation cascade [8].

In patients receiving enzyme therapy, these assessments should be performed every 3 months and at times of dosage modification (see Table 1). However, for patients who have reached their clinical goals and for whom there has been no change in the dose, the frequency of monitoring can be decreased to every 12 to 24 months.

Biochemical markers

Biochemical abnormalities secondary to bone or visceral involvement are common in patients with Gaucher disease. Thus, regular assessment of biochemical variables (Table 1) is of value in monitoring both the burden of the disease and the response to treatment.

The most prominent biochemical abnormality is the elevation of plasma chitotriosidase [30]. Levels of macrophage-derived chitotriosidase are dramatically elevated in the plasma of patients with symptomatic Gaucher disease. Furthermore, chitotriosidase activity correlates with the clinical parameters of disease severity and is reduced, but not normalised, in a dose-dependent manner by enzyme therapy [30]. Hollak and coworkers [30] have proposed that a reduction in chitotriosidase activity of less than 15% after 12 months of enzyme therapy, in combination with an insufficient response of at least one clinical parameter, should be a reason to consider a dose increase. Furthermore, a sustained increase in chitotriosidase at any point during treatment should alert the physician to the possibility of clinical deterioration and the need for dose adjustment. With the availability of a reliable assay for this enzyme, its correlation with disease burden and its sensitivity to treatment, chitotriosidase is a useful surrogate marker for monitoring children with Gaucher disease. However, clinical assessment must be used as the ultimate arbitrator when determining individualised dosing. A pitfall in the use of chitotriosidase as a marker of Gaucher disease that should be noted, however, is that 3%–5% of individuals in the general population have no activity due to the presence of a null allele in the chitotriosidase gene [9].

Serum levels of non-prostatic tartrate-resistant acid phosphatase (TRAP) [12,30] are also elevated in patients with Gaucher disease. The origin of TRAP in the sera of Gaucher patients is complex [1], but enzyme therapy has been found to lead to a relatively rapid, but often only partial reduction, in plasma TRAP activity [6].

Lysozyme and angiotensin-converting enzyme (ACE), levels of which increase in response to monocyte/macrophage activation, have also been used as plasma markers of Gaucher disease [30]. Active synthesis of ACE in Gaucher cells may be responsible for the elevated enzyme levels in the serum and spleen of patients with Gaucher disease, while high levels of lysozyme may reflect an increased body mass of reticuloendothelial cells. In 16 patients with Gaucher disease not receiving enzyme therapy, increases in serum levels in decreasing order were observed for chitotriosidase, neopterin, ACE, adenosine deaminase and beta-hexosaminidase [10]. However, chitotriosidase and TRAP seem to be the only markers that do not overlap between patients and controls [30]. One or more of the biochemical markers outlined above should be consistently monitored at least every 12 months.

Antibodies

About 15% of patients receiving enzyme therapy may develop antibodies to glucocerebrosidase. In most cases, seropositivity has little clinical effect and the antibody titre diminishes with continued therapy [43]. However, clinically significant inhibitory antibodies do occur and can lead to lack of response to enzyme therapy and/or clinical deterioration [49]. A sample for antibody testing should be obtained at baseline, and a subsequent sample at 6 months after beginning enzyme therapy is optional. The baseline and additional samples should be tested only if clinically indicated, such as for a suspected immune-mediated adverse event, prior to a switch to home therapy, or for suspected loss of enzyme therapy effectiveness.

Spleen and liver volume

Changes in liver and spleen volume are early and sensitive indicators of response to enzyme therapy. As such, organ volume measurement is valuable in assessing response to treatment and guiding dosage adjustment. In children receiving enzyme therapy, spleen and liver volumes should ideally be measured using MRI. MRI is an accurate and reproducible imaging modality that can be used to measure organs with irregular shapes. In addition, it can be used to detect infarcts, nodules, and other pathologies in the parenchyma that require additional evaluation or that will not respond to enzyme therapy. To measure liver and spleen volumes, simple, T1-weighted, contiguous, transaxial 10 mm sections are adequate, after which the outlines of each section should be traced [29]. The areas multiplied by the thickness gives the total organ volume. Routine MRI follow-up is recommended at 12-monthly intervals. When clinical goals have been reached at a stable dose of enzyme therapy, the frequency of volumetric MRI assessments can be reduced to 24-month intervals. Should MRI not be available, three-dimensional ultrasonography every 6 months can provide an approximation of spleen and liver volumes. Ultrasound also allows blood flow in the hepatic and portal veins to be measured.

Abdominal CT may also be used to assess spleen and liver volumes. However, it should be noted that this technique involves a significant inherent radiation burden and thus, should not be performed repeatedly in children. Supplemental techniques to assess spleen and liver volume include abdominal girth measurement; photographic documentation of the abdomen using a lateral view of the patient in his/her underclothes and palpation below the costal margin (verified by ultrasound).

Bone disease

Bone disease can occur without symptoms, particularly compression fractures of the spine, femoral head and calcaneous. Therefore, careful clinical monitoring is vital. The prevention of irreversible bone disease should be a major goal in the management of children with Gaucher disease, justifying regular bone assessment by MRI and/or other techniques, depending on the individual clinical situation (e.g. suspicion of a bone crisis) and availability of local facilities. Repeated exposure to X-rays should be minimised.

MRI should ideally be performed at baseline and, thereafter, every 12 to 24 months (if clinical goals have been achieved), before lowering the dose of enzyme therapy, after a change in dose or in specific acute circumstances, such as bone crises. Depending on clinical need, MRI may be required as often as every 6 months initially. Sedation or general anaesthesia may be necessary for children younger than 7 years of age to avoid motion artefacts [7]. At each visit, a sagittal, (lateral) T1-weighted scan of the spine and a coronal (anterior-posterior; AP), T1-weighted scan of the entire femur length (to assess for avascular necrosis of the femoral head or medullary infarcts) are recommended as a minimum. Coronal short tau inversion recovery sequences through the femora can provide additional useful information regarding bone marrow and soft-tissue oedema.

The apparent lack of deleterious long-term effects associated with MRI makes it appropriate for use in children with this chronic disease. However, it should be noted that differentiating normal haematopoietic marrow from Gaucher infiltration may be difficult in early childhood, due to age-related differences in composition (Fig. 1). Bone marrow in the spinal column and appendicular skeleton of young children is composed mainly of red bone marrow with a higher content of water in comparison to fat, which is gradually replaced by yellow bone marrow during childhood, adolescence and early adulthood [4,41]. The normal age-related expression of red marrow in these bones in children is quite variable, making the extent of marrow infiltration by Gaucher cells difficult to gauge. Therefore, caution must be exercised so that the developmental shift to

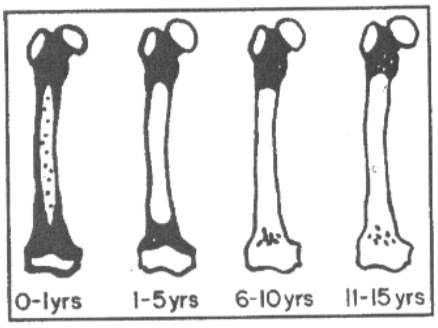

Fig. 1 Schematic representation of femoral marrow conversion with increasing age as seen on MRI images. Black areas represent red marrow; white areas represent yellow marrow or cartilage. Note that at 1 to 5 years, most diaphyses have a fatty marrow signal on MRI. Reproduced from [47] with permission

yellow marrow is not misinterpreted as response to treatment. Nevertheless, serial MRI examinations are helpful in documenting a response to treatment or progression to a more normal, age-related fatty or yellow marrow appearance.

When MRI is not available, a bone scan is a sensitive way to assess bone marrow infiltration throughout the body [27] and also has proven efficacy in diagnosing bone crises [35].

Plain radiography may be used for imaging orthopaedic complications such as fractures, and detecting focal lesions such as avascular necrosis. This technique has the advantage of being widely available and inexpensive. However, it is relatively insensitive for defining the pattern of skeletal disease and lesions may not show a response to therapy for a number of years. Because of this, plain radiography cannot be used by itself to monitor the skeletal response to therapy and should only be used in conjunction with MRI investigations.

The minimum recommendation for routine follow-up using plain radiography is an X-ray film of the chest, pelvis and long bones. Spinal X-ray films can be recommended only when the patient is symptomatic, when disease is severe, there is poor growth or kyphosis is developing. Nevertheless, some clinicians may prefer a whole-body survey for comparison with later developments and symptoms, whilst those with reservations about the sensitivity of the technique might choose to exclude the skull, hands and feet to limit exposure to radiation. Local experience and preferences should allow for some flexibility in approach. Radiographic abnormalities of the skeleton are, in general, late findings of disease progression, and are much less sensitive to Gaucher disease changes than MRI or radionuclide scans.

BMD analysis by dual-energy X-ray absorptiometry (DXA) of the femoral neck and spine should ideally be performed annually until therapeutic goals are met and at 24-month intervals thereafter. Although DXA is sensitive to generalised osteopenia and may prove useful in monitoring the response to long-term enzyme therapy, this technique does not detect local bone changes, so it cannot be reliably used to evaluate fracture risk. In addition, unrecognised vertebral collapse can give falsely high BMD measurements in the spinal column. Ideally, a contemporaneous spinal MRI should be performed; if this is not possible, an AP X-ray film of the spine or a bone scan can be performed. The value of DXA is also dependent on the availability of comparative measurements from healthy age- and sex-matched controls [20, 31, 39].

Pulmonary and cardiovascular function

Clinically significant lung disease is rarely associated with non-neuronopathic Gaucher disease [21] and pulmonary hypertension has so far not been described in children. Nevertheless, rare cases of pulmonary infiltration may be encountered. Consequently, the lungs should be assessed at 12-month intervals by chest X-ray film and simple pulmonary function tests. Suspected pulmonary involvement can be semi-quantitated using a high-resolution chest CT scan.

Quality of life

Gaucher disease has a considerable negative impact on QoL [4, 18, 19, 22,2640]. It is recommended that functional health and well-being assessment should be performed annually. Although the Short-Form 36 (SF-36) Health Survey [48] is of limited value in very young patients, it is currently used by some centres. However, other centres have developed their own QoL scoring systems and there is a clear need for a validated QoL assessment tool for use in paediatric populations with Gaucher disease. Psychosocial well-being should be monitored through regular discussion with the patient and his/her parents.

Pain

Pain is generally related to bone disease; nevertheless, MRI findings of presumed medullary infarcts may be asymptomatic. Splenic infarcts may also be a considerable source of pain. The occurrence of pain should be monitored by careful questioning of the patient at each clinic visit. As for the baseline assessment of pain, facial pain scales, developed specifically for children, can be useful in assessing pain severity [28].

Monitoring of asymptomatic children not receiving enzyme therapy

Asymptomatic children who have been identified as having non-neuronopathic Gaucher disease (possibly as a result of screening the siblings of a symptomatic child), but who are not receiving enzyme therapy,

should also be monitored regularly. Ideally, this should include a physical examination and assessment of growth at 6-month intervals and annual analyses of haematological and biochemical parameters. In addition, these patients should undergo MRI and DXA examination every 24 months to detect any bone-marrow infiltration or osteoporosis/osteopenia. Early treatment of such patients at the onset of any clinical symptoms or signs should help to minimise the impact of the disease.

Summary

The paediatric manifestations of non-neuronopathic Gaucher disease are underrecognised. The majority of recommendations and methods for monitoring the disease have concentrated on the management of adult patients, and there is a lack of information in the literature on how best to monitor and treat the disease in children. The recommendations provided here give guidance on how to treat and monitor children with non-neuronopathic disease. Regular comprehensive assessment of the QoL of patients with the disorder, and of their haematological, visceral, growth and skeletal manifestations, along with the individualisation of therapy, will contribute to optimising patient outcomes.

Acknowledgements This publication was supported by an educational grant from Genzyme Corporation.

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