Review

Orthopedic considerations in Gaucher disease since the advent of enzyme replacement therapy

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ABSTRACT Gaucher disease, the most prevalent lysosomal storage disorder, is characterized by hepatosplenomegaly, hypersplenism, and rarely, neurological involvement. The most variable symptoms relate to skeletal disease, and both onset and progression are difficult to predict on the basis of genotype. This review describes findings from a large referral clinic (> 500 patients) and from the literature in the decade since the advent of specific enzyme replacement therapy. Such therapy is effective in reducing visceral and hematological involvement, but its greatest advantage as regards the skeleton is prevention of irreversible damage. Avascular necrosis of the joints—particularly the hips but also the knees and shoulders—and pathological fractures of the long bones including the ribs, as well as episodic "crises' of bone pain in children and young adults, are common manifestations. Various imaging modalities should be performed at baseline for life-long monitoring, and then as required because of specific complaints. Surgical interventions such as joint arthroplasties are important adjuvant treatments in this population; presurgical hematological profiling plus antibiotic cover and postoperative pain control are equally critical. Opportunities for orthopedic consultations with senior surgeons are not abused by our patients. These reflect disease-related morbidity, with greater numbers of requests being made by patients requiring enzyme therapy, who by definition have more severe disease characteristics.

Gaucher disease, the most prevalent lysosomal storage disorder, is caused by a genetic defect in the enzyme β-glucocerebrosidase (EC 3.2.1.45) and the consequent accumulation of a glycolipid, glucocerebroside, in cells of the monocyte-macrophage system, the "Gaucher cells" (Figure 1). The genomic region near the β-glucocerebrosidase locus on human chromosome 1q21 includes its pseudogene and several other gene loci. Of the more than 200 mutations identified, most have been unique or rare mutations. Those with some prevalence have been loosely categorized as being mild, severe, or lethal mutations on the basis of residual enzyme activity and clinical phenotype, and as being sporadic or polymorphic, on the basis of haplotyping (Grabowski and Horowitz

Figure 1. Massive hepatosplenomegaly as a presenting sign of type I Gaucher disease.

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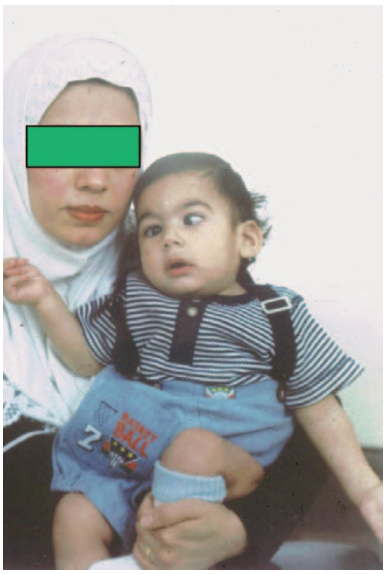

Figure 2. Horizontal gaze palsy in a child with type II Gaucher disease.

1997). To date, DNA-based analysis for correlation of genotype and phenotype, which would greatly enhance prognostication and facilitate medical care of patients at risk of deterioration, is imperfect.

The most common symptomatic presentation includes hepatosplenomegaly (Figure 1), anemia, and thrombocytopenia (Beutler and Grabowski 2001). Bone involvement is perhaps the most variable of all the symptoms attributed to Gaucher disease. This can range from asymptomatic disease with or without radiological signs, to symptomatic disease including avascular necrosis of the large joints and pathological fractures (e.g. compressed fractures of the spine), which can be severe and cause considerable pain and disability.

Classically, Gaucher disease has been divided into three clinical types based on the absence or presence of neurological involvement. Type I is defined by absence of neurological involvement and usually the presence of the N370S (1226G) mutation on at least one allele. Although panethnic, it is especially prevalent among Ashkenazi Jews (1:850 live births). Types II and III, both relatively rare and panethnic, are marked by involvement of the central nervous system (Beutler and Grabowski 2001). Horizontal supranuclear gaze palsy is pathognomonic for the neuronopathic forms (Figure 2). Patients with the acute neuronopathic form, type II, do not survive long enough to manifest skeletal complications, but earlier surveys in the non-neuronopathic type I patients have reported substantial evidence of bone involvement in 21–83% of patients (Matoth and Fried 1965, Beighton et al. 1982, Kolodny et al. 1982, Zimran et al. 1992). In the subacute neuronopathic type III patients, the incidence ranged from no bone disease in the Arab IIIc-variant patients (Abrahamov et al. 1995) to 100% among the Norbottnian-variant patients (Svennerholm et al. 1982).

More recently, an international registry has culled the symptoms and signs of patients from countries worldwide. Of 1028 patients from 25 countries with up to 5 years of follow-up, 633 (62%) had some form of bone disease radiologically (Charrow et al. 2000, Weinreb et al. 2002), with 437 of those patients (43%) complaining of some form of bone pain (Weinreb et al. 2002).

With the advent of enzyme replacement therapy (ERT; Barton et al. 1991), which has proven to be safe and effective in improving the hematological parameters and reducing the organomegaly, it was hoped that the bone disease would be equally amenable to this therapy. The general experience, however, has been that the skeletal response is considerably slower (Hill et al. 1993, Pastores and Einhorn 1995, Rosenthal et al. 1995) and it is unclear whether destructive lesions are reversible (Sidransky et al. 1994, Elstein et al. 1997). Even so, it does seem that bone crises are much less frequent among ERT-treated patients and that severe skeletal complications are usually prevented if ERT is begun at an early age in patients at risk (Elstein et al. 1998). In addition, because of cost considerations, many national health budgets are unable to acquire ERT for affected patients and these individuals continue to suffer from the consequences of the natural history of their disease. Thus, the need for orthopedic consultations and interventions is as critical today as it was in the era prior to global marketing of ERT.

The objective of this survey is to describe the range of orthopedic manifestations of Gaucher disease as experienced today, one decade after the availability of ERT, in a very large referral – and also to review the literature (Samuel et al. 1994, Elstein et al. 1996, Pastores et al. 1996, Ciana et

Table 1. Survey of original studies (excluding case reports and reviews) of skeletal involvement since the availablity of enzyme replacement therapy (ERT), 1994–2004

Citation	Patients	Results	Conclusions
Samuel et al	5 teens on APD [a]	Decrease in bone crises to 0 in 3, and in 2 from 1–3/year to <1/year; only 1 pathological fracture in 1	Efficacy of APD and possibility for use in inducing "remissions"
Elstein et al	25 (14 on ERT)	All had decreased bone mass; ERT-treated had less bone pain; one patient in each group developed avascular necrosis; cortical bone thickness improved with ERT over 2–4 years	ERT improved bone thickness even in osteoporotic, splenectomized adults; recommend early intervention in children at risk for skeletal disease
Pastores et al	61	Mean bone density at each skeletal site was significantly lower than age-/sex-matched. Severity of osteopenia correlated significantly with disease severity	Bone density measurements provide quantitative assessment of bone involvement
Ciana et al	5	Patients with severe bone involvement treated with pamindronate and calcium; all had decreased bone pain and decreased markers of bone resorption plus increased bone density at 3–5 months	Pamindronate is effective , with no important side effects for severe bone involvement
Allison et al	3	All showed improvement in marrow MR signal consistent with some reconversion to fatty marrow with ERT	MR can be utilized to monitor effects of ERT
Cohen et al	10 on ERT	No fractures occurred but bone crises continued thru fifth year	Low-dose ERT prevented fractures but not bone crises
Ida et al	35	Significantly higher prevalence of severe bone disease in splenectomized patients: 81% vs 21% in nonsplenectomized. 4/14 on ERT or after bone marrow transplantation manifested bone involvement first during/ after treatment	Splenectomy may correlate with accelerated skeletal deterioration; "ERT dosages should be based on disease severity and on age, with sustained administration of full doses in patients at greater risk of important skeletal complications."
Kocher & Hall	4 (2 each: kyphotic deformity and without neurologic compromise)	Recommend anterior spinal release with fusion and posterior spinal fusion with segmental instrumentation for kyphotic deformity; in spinal cord compromise at apex of kyphotic deformity with retropulsion of involved bone, anterior decompression is required	Recommend early intervention before severe deformity and neurologic compromise
Poll et al	30 on ERT	63% showed increased signal intensity on T1- and T2-weighted images after 36 months ERT; nonhomogeneous patchy signal intensity correlates with infarcts	MRI (T1- and T2- weighted spin-echo sequences) is a valuable, non-invasive method for monitoring
Altarescu et al	21 type III on ERT	Improved bone structure comparable to type I on ERT	Very high-doses used with good clinical results and putative cognitive effect
Drugan et al	16	Significant decrease of osteocalcin (11.1 ± 2.3 ng/ml) and type I collagen C-terminal telopeptide (3617± 536 ng/ml) in Gaucher disease, compared to controls	Serum markers of bone turnover can be an auxiliary tool in diagnosis, staging, and monitoring skeletal lesions
Schiffmann et al	29 on ERT, no spleen	Bone density by single-energy CT (P = 0.001) and dual-energy CT (P = 0.06) declined overall; no significant difference due to added calcitiol.	ERT alone, or with calcitriol, cannot repair bonestructure in splenectomized adult patients
Aharoni et al	11 (4 on ERT)	All but 1 patient had increased (99m)Tc-Sestamibi uptake in bone marrow. No correlation noted between uptake and severity score, radiographic changes, densitometry, or treatment status	(99m)Tc-Sestamibi scanning is sensitive for detection of bone marrow deposits, but inadequate for identification of risk for skeletal complications or follow-up of ERT.
Maas et al	30 untreated	Fat fraction (correlated with liver size) ranged from 0.08–0.40 (mean=0.20). Bone complications occurred primarily in patients with fat fraction < 0.23.	Fat fraction of lumbar spine when measured with Dixon QCSI correlates with bone complications
Mariani et al	74 (31 on ERT)	(99m)Tc-Sestamibi scintigraphy showed that 71/74 patients had bone marrow involvement; The scintigraphic score correlated with overall clinical severity score	(99m)Tc-Sestamibi uptake reliably identifies bone marrow infiltration by Gaucher's cells.

[a] APD aminohydroxypropylidenebisphosphonate

Figure 3. Ehrlenmayer flask deformity is nearly an universal finding (even in young children with type I Gaucher disease).

al. 1997, Allison et al. 1998, Cohen et al. 1998, Ida et al. 1999, Kocher and Hall 2000, Altarescu et al. 2001, Poll et al. 2001, Aharoni et al. 2002, Drugan et al. 2002, Maas et al. 2002, Schiffmann et al. 2002, Mariani et al. 2003) (Table 1).

Bone pathology in Gaucher disease

Infiltration of bone marrow by Gaucher cells results in displacement of the bone marrow, inducing a shift in hematopoetic activity from proximal to more distal sites (albeit with epiphyseal sparing). This process can involve almost any long bone, but surprisingly there appears to be no pattern to site prevalence, nor to the degree to which any individual may be affected. Indeed, to date there are no markers for prediction of onset or progression of bone involvement. Once begun, the deterioration from osteopenia to osteonecrosis is overtly comparable to that in persons who do not have Gaucher disease. Also, as in other individuals with one osteonecrotic and painful hip joint, ipsilateral damage of the knee or of the contralateral hip is common. However, there exists an unexplained conundrum: skeletal disease does not seem to be correlated with Gaucher cell burden (as massive infiltration may be seen in bone marrow aspirates or biopsies from patients with no lesions or osteoporosis), and although ERT alleviates bone pain (and early intervention may be posited to prevent initiation of the events that lead to bone destruction), ERT does not necessarily reduce Gaucher cell infiltration of the bones. This is an active area of research.

Hermann et al. (1986) formulated a 5-stage classification of Gaucher bone lesions in type I Gaucher disease: stage 1, diffuse osteoporosis; stage 2, medullary expansion; stage 3, osteolysis; stage 4, necrosis/sclerosis; and stage 5, destruction and collapse. Thus, the Ehrlenmeyer flask deformity of the distal femur (Figure 3) and the proximal tibia (stage 2) is among the earliest signs which, although not pathognomonic of the disease, is seen in most patients at presentation along with osteoporosis. Medullary expansion and osteolysis may also result in lytic lesions and/or poorly healing fractures. Marrow sclerosis may presage osteonecrosis (Figure 4) and collapse, this being the common pathway of avascular necrosis of both the large and small joints.

Sites involved in Gaucher disease

The mandible is not readily identified as a site of Gaucher disease, although case reports from the dental literature have long ago shown Gaucher cell infiltration on panoramic jaw radiographs (Weigler et al. 1967). The most prevalent findings are gross widening of marrow spaces, frank radiolucency, endosteal scalloping, cortical thinning, root resorption, and inferior displacement of the mandibular canal or effacement of its cortices (Carter et al. 1998). Nonetheless, dental caries are no more prevalent in this population (Carter et al. 1998).

The upper extremity, being non-weight bearing, is often unrecognized as a presenting site of Gaucher-related pain and destruction (Figure 5). In a series of 55 children and adolescents, one third presented with upper limb pain, with osteopenia and thinning of the cortex in the hands of half of these patients (Katz et al. 1993a).

The spine is often affected (Figure 6). Among the earliest explanations for the unusual "step-off", "H-type", or "fish-mouth" vertebral endplate deformation (Figure 7) as described in 4 patients 25 years ago, was collapse of the vertebral body and subsequent growth recovery peripherally (Schwartz et al. 1979). Today, these defects are not uncommonly seen in the thoracolumbar spine, yet generally do not induce spinal deformation and

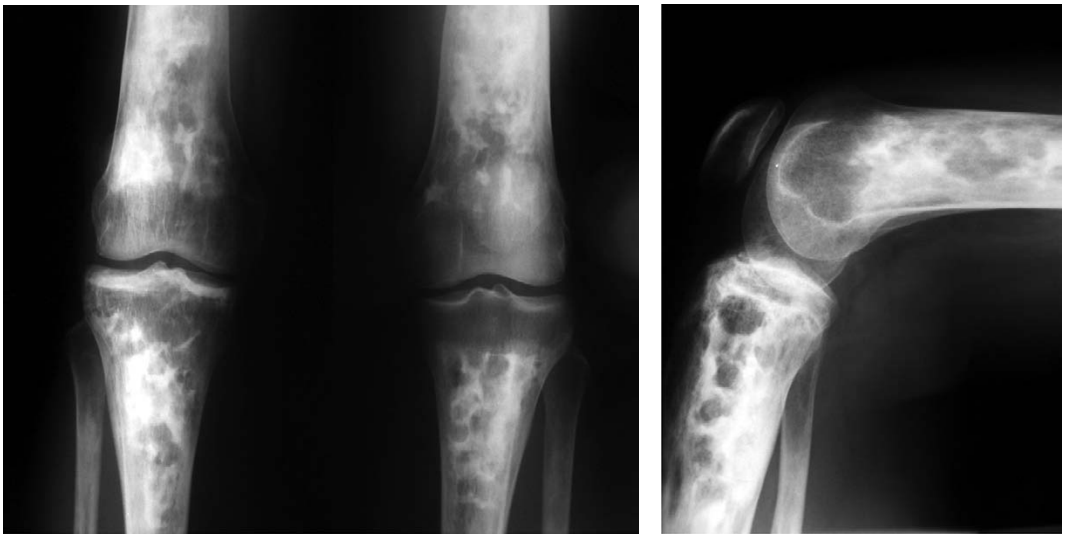

Figure 4. Marrow sclerosis and lytic lesions in a splenectomized young adult.

Figure 5. Pain in the shoulder as a presenting sign of skeletal involvement.

Figure 6. A 21-year old patient with type I Gaucher disease.

hence—unless there is cord compression and/or neurological signs—no intervention is recommended. Thoracic kyphosis and vertebral collapse in children is well documented in type I disease (Ruff et al. 1984, Katz et al. 1993b). We have also seen gibbus in a child with type IIIb disease (Figure 8) and in a young woman with type IIIc disease (presenting after mitral valve replacement) that was progressive, but the vertebral bodies were not deformed.

The ribs are sites of pathological fractures that we have described as "romantic fractures" (Elstein et al. 1997) since the most common etiology is a hug from the patient's loved ones.

A very rare site of osteonecrosis in general is the sacroiliac joint, but this too has been seen in Gaucher disease (Bisagni-Faure et al. 1992) with magnetic resonance imaging demonstrating an area of high signal intensity in the iliac part of the right sacroiliac joint, and a periosseous collection of

Figure 7. 'H'-type vertebral endplate deformation.

Figure 8. Gibbus in a 10-year old girl with type IIIb Gaucher disease but without vertebral deformation.

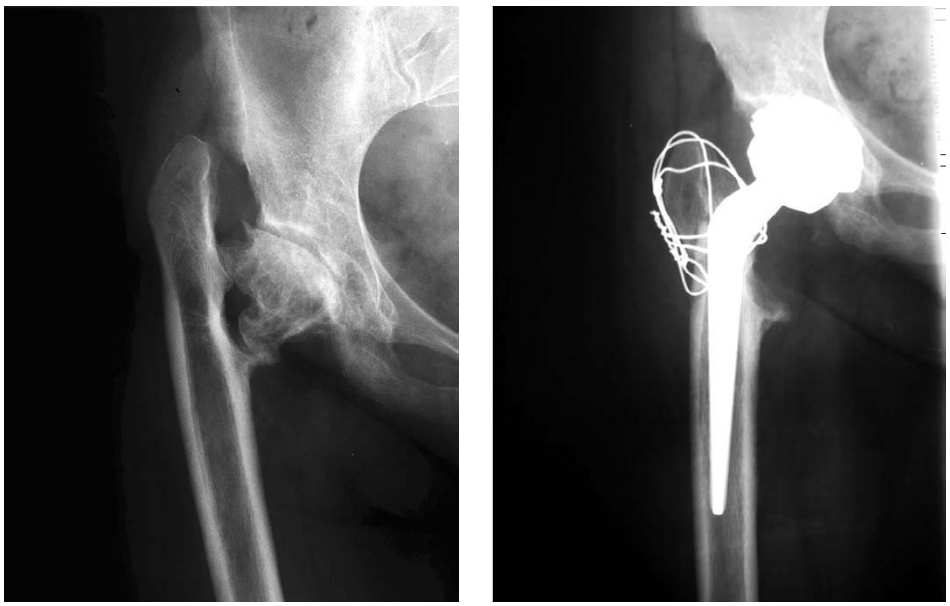

Figure 9. Total hip replacement to improve mobility and pain in a 38-year old woman.

blood. On bone scan, marked differences between the parts of the joint can be discerned (Aharoni et al. 2001).

Hip problems (often bilateral) are common (Schein and Arkin 1973), and although not dramatically affected by ERT, surgery has improved the functional outcome (Figure 9). In this context, it is also worth mentioning that splenectomy (Figure 10), which in the pre-ERT era was the mainstay of clinical management of massive splenomegaly

Figure 10. Because of refractoriness to enzyme therapy due to multiple infarctions, this (12 kg) spleen with removed from an adult patient with Gaucher disease.

Figure 11. Unicondylar knee replacement due to medial compartment damage in a splenectomized adult patient.

Figure 12. Foot and ankle involvement with unremitting pain in an adult non-splenectomized man.

and its attendant hypersplenism (and growth retardation in children), has been obviated by enzyme replacement. Yet, it is important to emphasize that in patients who have been splenectomized prior to ERT and/or for whom ERT is unavailable, there is an attendant risk of increased bone disease consequent to total splenectomy (Rose et al. 1982, Fleshner et al. 1991) or even partial splenectomy (Zimran et al. 1995).

Knee involvement (Figure 11) requires a high degree of clinical suspicion as a site of AVN or pathological fracture in Gaucher disease, and also the choice of the correct imaging techniques to document the source of unremitting pain (Zanzi et al. 1988), even in patients receiving ERT (Lebel et al. 2003). Similarly, the ankle or foot (Figure 12) may be the sole expression and/or presenting sign of Gaucher-related bone disease, even in adolescents (Katz et al. 1999). In older patients for whom these bone complications appear as a sole presenting symptom, however, other non-Gaucher related causes should be investigated at the same time.

Arthritic-like hand and/or foot pain concommitant with initiation of ERT treatment is an interesting but unexplained phenomenon. This reactive or adjuvant-like arthritic reaction is especially frustrating in patients for whom bone pain is an indication of ERT, but may be of sufficiently severe nature to induce some patients to halt ERT until the symptoms have abated.

As previously mentioned, bones do not appear to respond to ERT on the same time scale or dosage continuum as the viscera or hematological parameters (Rosenthal et al. 1995, Elstein et al. 1996). In a recent case report, a child was given increasing doses of ERT in order to quickly induce improvement in bone complaints (Larsen et al. 2003). As discussed in a commentary on this case, immediate relief could not be expected and dissatisfaction with the lack of immediate response was not justified (Beutler 2004).

Other forms of bone involvement in Gaucher disease

The early literature is replete with reports of patients for whom osteomyelitis was an overwhelming complication (Yossipovitch et al. 1965). Today, however, bone infections are quite rare; invasive draining techniques introduced because of

a bone crisis may be the cause of local bone infections (Figure 13) (Noyes and Smith 1971, Elstein et al. 1997).

Based on magnetic resonance imaging, Horev et al. (1991) suggested that sub-periostal hemorrhage or hematoma in the bone may explain the phenomenon of acute bone pain "crises" (Figure 14). We feel that this is true since ERT has dramatically reduced the incidence of bone crisis (Poll et al. 2002); but while others have attributed the diminution in crises to an ERT effect on bone, we believe that ERT improves thrombocytopenia and reduces the tendency to bleeding so that there are fewer incidents of hemorrhage/hematoma in the bone, and hence fewer crises.

Also, hematoma/abcesses of the muscle (Jmoudiak et al. 2003) or extraosseous manifestations (Poll et al. 2000) which may mimic malignancy (Hermann et al. 1994) are important differential diagnoses.

Imaging modalities for skeletal involvement

The plain radiographs, including at least the chest, thoracolumbar spine, all four limbs and pelvis, should be considered part of the routine work-up at presentation (Myers et al. 1975), and also for long-term follow-up (Elstein et al. 1997).

MRI in Gaucher disease (Hermann et al. 1986, 1994) accurately depicts marrow and soft tissue damage secondary to infarction (Figure 15) and provides a crude estimate of the burden of Gaucher cells in the marrow. It should be used as a diagnostic adjunct in those patients with pinpointed skeletal involvement, e.g. assessment of AVN or spinal compression. For the spine, T1- and T2-weighted images in coronal and axial planes, and sagittal planes should be taken (Cremin et al. 1990). As mentioned above, MRI has also been used for documentation of bone crisis (Horev et al. 1991). MRI is sensitive to osteonecrosis, and may define the extent of these changes even in the symptom-free patient. Finally, MRI, although incapable of quantitative assessments, does not have any radiation hazard and hence is a better technique for life-long monitoring of these chronic patients. It is therefore the preferred mode of routine follow-up in centers in which this modality is not considered a scarce resource. An international expert panel recommended the use T1- and T2-weighted magnetic

Figure 13. A single episode of bone pain in a 16-year old and local draining resulted in osteomyelitis of the tibia; a few years later avascular necrosis of the hip necessitated replacement.

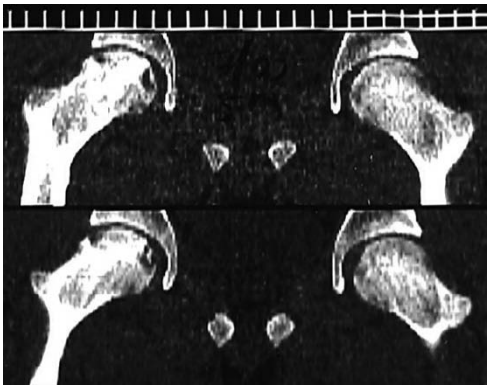

Figure 14. Series taken during the course of a bone "crisis" in a 20-year old man with a history of bone pain since age 14 years.

Figure 15. MR imaging of an bone infarct in a 15-year old boy who had been receiving enzyme therapy for 11 years.

resonance imaging of the entire femora and plain radiography of the femora, spine, and symptomatic sites for orthopedic complaints as well as initial diagnosis (Johnson et al. 1992). Follow-up skeletal and visceral assessments were recommended every 12–24 months in untreated patients, and every 12 months—and/or at changes in ERT dosage or frequency schedules—in treated patients.

Quantitative chemical shift imaging (QCSI) has been suggested to be superior to MRI (Hollak et al. 2001), in that it accurately estimates the displacement of normal marrow by lipid-laden Gaucher cells by comparing the differential (proton) signaling of water to fat (triglyceride fraction), especially in the lumbar spine—and particularly for monitoring the effect of ERT on bones (Rosenthal et al. 1989, Maas et al. 2002). Nonetheless, this modality is a rare resource in most countries.

Computed tomography (CT) has also been suggested as a marker of disease severity (Catronovo et al. 1993), based on the ability to track Gaucher cell infiltration and based on studies of improvement following transplant-induced restoration of marrow function. However, conventional CT is incapable of quantitative assessment and is associated with significant radiation, making it a less appropriate choice for frequent follow-up examinations. High-resolution quantitative CT employing both single (SEQCT) and dual energy (DEQCT) calculations, as measures of trabecular and cortical bone density in addition to marrow fat content, show poor correlation with MRI (Castronovo et al. 1993). Thus, CT may be an imperfect means of assessing bone disease parameters in Gaucher disease.

More esoteric means of ascertaining skeletal damage include inhalation of radiolabeled lipid-soluble xenon gas (133Xe) for bone infarcts (Charrow et al. 1998), technetium-99m sestamibi (99mTc-MIBI) as an indicator of cellular density and metabolic activity, and technetium-99m hexametazime (99mTc-HMPAO) as an indicator of fat infiltration (Mariani et al. 2003). Again, these are rare resources of limited prognostic advantage (Drugan et al. 2002).

Dual energy X-ray absorptimetry (DEXA) for assessment of bone density is valuable in diagnosing osteoporosis, and has also been investigated as a potentially useful means of evaluating skeletal involvement in Gaucher disease (Pastores et al. 1996).

Modes of orthopedic intervention

Hopefully, curative approaches to Gaucher disease such as gene transfer will alter the natural history, so that patients will no longer be affected by skeletal complications. In the past and even now, however, the morbidity due to severe bone involvement is of primary concern to both patients and physicians since severe skeletal disease invariably leads to appreciably diminished quality of life and often severe disability. The recommendation in a 1988 study of successful total hip replacements was that this was the treatment of choice for AVN in Gaucher disease (Goldblatt et al. 1988). Among the problems encountered at that time were risk of infection and bleeding, concern about cemented prostheses in bone which was both damaged and likely to continue to disintegrate (van Wellen et al. 1994), and inability to predict outcome in young patients (Alkali et al. 1979). Nonetheless, more recent experiences (Tauber and Tauber 1995, Lebel et al. 2001) have shown that meticulous attention to antibiotic cover and hematological stability ensure an excellent outcome in patients with Gaucher disease, which is comparable to that in other patients with an equal degree of disability and/or pain. Similarly, shoulder, knee and ankle reconstruction or replacement surgery, and even revision surgery, are safe for patients with Gaucher disease.

Drilling into the bone of an affected joint is an option employed by us with the rationale that Gaucher cell infiltration induces compromised vascular supply and decreased oxygen supply to joints. Surprisingly, drilling often gives long-term pain relief and improved functional mobility, with little added risk of fracture. However, more experience is required before definitive data are available.

Presurgical preparation

Before surgery, patients with Gaucher disease should undergo a hematological work-up including hemoglobin, platelet counts and aggregation, coagulation factors, and possibly a thrombophilia profile so that appropriate and adequate blood products are ordered in advance. (This applies equally to dental surgery and even dental cleaning of plaque, both of which are procedures with expected loss of blood and risk of hemorrhage.) Poor platelet function is relatively common in

Table 2. Orthopedic consultations at the Gaucher Clinic, SZMC

	ERT patients	Non-ERT patients	Total
Number patients	123 (26%)	356 (74%)	479
Requesting consultation	61/115 (53%)	54/115 (47%)	115/479 (24%)
Orthopedic consultations	270/365 (74%)	95/365 (26%)	365
Age at consultation (years)			
0–20	68 (77%)	20 (23%)	88/365 (24%)
21–40	83 (70%)	35 (30%)	118/365 (32%)
41–60	102 (74%)	35 (26%)	137/365 (38%)
> 61	17 (77%)	5 (23%)	22/365 (6%)
Site of complaint			
Hips	41 (72%)	16 (28%)	57/365 (16%)
Knee	27 (59%)	19 (41%)	46 /365 (13%)
Ankle	9 (75%)	3 (25%)	12/365 (3%)
Spine	21 (60%)	14 (40%)	35/365 (10%)
Rib	6 (75%)	2 (25%)	8/365 (2%)
Wrist	2 (40%)	3 (60%)	5/365 (1%)
Shoulder	17 (68%)	8 (32%)	25/365 (7%)
Other	46 (71%)	19 (29%)	65/365 (18%)

Gaucher disease (Gillis et al. 1999), and is an important preoperative consideration.

Pain management

Adequate pain control for bone pain is essential, be it episodic or chronic, including narcotics when indicated – even in adolescents (Elstein et al. 1997). Bone pain, when it is a presenting sign or a sole manifestation of Gaucher disease in a child or adolescent, may wane as the patient grows, and thus maximal pain relief should be advocated. NSAIDS and other over-the-counter formulations may be adequate. Steroids, however, have limited, if any, value for the patient with Gaucher disease who is at risk of osteopenia and osteonecrosis.

The use of orthopedic consultations in a referral clinic

During the past decade, there has been an open-door policy for patients of the Gaucher Clinic to be seen by senior orthopedic surgeons (MI and EL). At the time of the survey, 479 patients, of whom 123 (26%) have been or are currently being treated with ERT, were being seen at annual or bi-annual follow-up visits. Table 2 presents the results of a survey of areas of complaint presented for orthopedic consultation.

Visits to orthopedists by citizens in the United States increased from 11% of all visits in the mid-1970s to 15% in the mid-1990s. More than 28% of visits are related to injuries (Schappert 1998). Patients with Gaucher disease have legitimate concerns for bone involvement since it is an important sign of their disease. However, skeletal complaints vary, and of course, may not be related to Gaucher disease. It appears that patients with Gaucher disease who do not require ERT, and hence by definition have milder disease, rarely require excessive orthopedic consultations. Among untreated patients, there were only 95 consultations among 54 individuals, including injury-related events, i.e. an average of 2 consultations for only 15% of the untreated cohort over a 10-year period. ERT patients requested more consultations than untreated patients, but these were generally related to Gaucher-specific sites (Table 2).

At our clinic, hip problems were the most common among ERT patients. This includes osteonecrosis and hip replacement, even among younger patients. In contrast, knee problems were the most common among the untreated patients, particularly older patients, and pain was the chief complaint, mostly not related to radiological evidence of damage. Thus, it may be surmised that, in general, the ERT patients do have more orthopedic problems, and that the need for orthopedic specialists is high even among children and teenagers. Although some of our untreated patients of all ages have requested orthopedic consultations, only a few have had signs or symptoms of Gaucher disease.

Summary

Gaucher disease is characterized by phenotypic heterogeneity, both in terms of age of onset and in terms of the degree and progression of visceral and skeletal involvement. Nonetheless, generally speaking, it may be suggested that patients with early involvement are at risk of skeletal disease, the nature and extent of which are equally unpredictable. Patients at risk may benefit from early intervention with ERT, although most lesions and osteonecrosis are irreversible. ERT is not universally available. Orthopedic management remains an important aspect of care in Gaucher disease, and in our experience, despite the chronicity of skeletal disease, patients do not abuse the opportunity for orthopedic consultations.

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