

# Low-dose High-frequency Enzyme Replacement Therapy Prevents Fractures Without Complete Suppression of Painful Bone Crises in Patients with Severe Juvenile Onset Type I Gaucher Disease

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**ABSTRACT:** Patients with type I Gaucher disease often present as adults with a mild disease and with less severe genetic mutations, especially 1226G/1226G (N370S/N370S). Patients presenting as children have an excess of compound heterozygotes of N370S and other mutations, such as 84GG, 1448C (L444P) and IVS2+1 in whom bone disease is common. We report our experience with low-dose high-frequency enzyme replacement therapy in such severely affected children. Ten patients (with severe juvenile onset type I Gaucher disease) were treated. Alglucerase (Ceredase®) was infused at 30 units/kg/month in 13 fractions/month for more than one year. Bone disease was used as the main criterion for evaluating treatment results. No fractures occurred in spite of the fact that bone crises occurred in four patients after 12 to 24 months of treatment, in two during the third year, and in one during the fifth year. Nonosseous manifestations improved with treatment. The ability of low-dose high frequency alglucerase to prevent fractures in the presence of continuing bone crises was demonstrated.

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## INTRODUCTION

Gaucher disease is an autosomal recessive metabolic disorder characterized by the abnormal accumulation of glucocerebroside in the reticulo-endothelial cells due to deficiency in glucosyl-

ceramide- $\beta$  glucosidase activity (1). The disease is divided into three types: **Type I**, non-neuronopathic, so-called adult Gaucher disease, is the most common, marked by splenomegaly associated with various degrees of pancytopenia. The infiltration of the bone marrow by Gaucher

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cells causes multiple skeletal manifestations, especially bone pain (35 to 83%) of patients (2,3). The pain is usually nonspecific and dull and persists from one to two days (2). Severe pain due to so-called bone crisis (23 - 37% of patients) and pain associated with pathological fracture, osteomyelitis and degenerative joint disease also occur (2,4-6). A subpopulation with a more severe phenotype which we have defined as "severe juvenile-onset variant" will be discussed later in this report. **Type II**, acute neuropathic Gaucher disease, appears in infancy and is associated with severe neural abnormalities. Average survival is nine months. **Type III**, subacute neuropathic Gaucher disease, is characterized by hepatosplenomegaly appearing in the first decade of life and neurological and skeletal manifestations during childhood and adolescence. The majority of affected patients have convulsions (1).

Episodes of so-called bone crises are among the most troublesome manifestations. The crises may last from one to several weeks (5,6), are characterized by severe pain often unrelieved by narcotics, associated with local signs of redness, swelling, warmth and tenderness around the involved bone, and often fever (6). They tend to be recurrent. Histological and radiographic studies have suggested that the crises are clinical manifestations of osteonecrosis (5). Crises have been reported in all the long bones, the spine, pelvis and hands. Most common are crises of the femoral head, which is usually the earliest clinical manifestation of femoral head osteonecrosis (7). Pathological fractures may follow these bone crises especially in long bones (4).

Although the radiograph shows no bone changes at the onset of crisis, the bone scan initially shows an area of decreased uptake, followed by increased activity six weeks later (8). The MRI scan shows a high intramedullary and subperiosteal signal on both T<sub>1</sub>- and T<sub>2</sub>-weighted sequences, suggesting a subacute hemorrhage or hematoma (9).

Enzyme replacement therapy with alglucerase (*Ceredase*®, Genzyme, Inc., Massachusetts) for

type I Gaucher disease is directed at retarding and reversing the accumulation of glucocerebroside. Regression of organomegaly and improvements in height, weight, sexual maturity, hematological parameters, liver function tests, skeletal abnormalities, and pulmonary manifestations have all been demonstrated (10-14). However, the appropriate dose remains controversial. The treatment regimen suggested by Barton et al (15) of 60 IU/kg body weight per infusion biweekly is convenient but extremely expensive. Beutler (16) suggested that if 30 IU/kg body weight/month were fractionated into 13 doses/month, it would be possible to treat four times as many patients for the same cost without compromising treatment efficacy. Initial reports have indicated that this may indeed be true (13,14).

## MATERIALS AND METHODS

Since 1960, 73 Jewish Ashkenazi patients with type I Gaucher disease have been routinely followed at our Institution. Between June 1992 and July 1993, ten children and young adults (seven females, three males) with severe juvenile onset type I Gaucher disease were placed on enzyme replacement therapy alglucerase, 30 IU/kg body weight/month fractionated into 13 doses/month, as suggested by Beutler (16). Eight had genotype N370S/84GG and two, N370S/L444P. Patient 1 had started to receive 30 IU/kg/month for several months at another center. Criteria for diagnosis of the juvenile onset variant were young age at presentation, large spleen and liver, growth retardation at diagnosis, young age at splenic resection, and the occurrence of bone crises. One patient presented at age 6.5 months, three at age of 3 years, and six at age 3 to 6 years. At presentation the spleen was palpable at less than 6 cm below the costal margin in four patients, at 6 to 10 cm in four, and at more than 10 cm in two. The liver was palpable at less than 3 cm below the costal margin in one patient, at 3 to 6 cm in seven, and at more than 6 cm in two. Bone age was delayed more than two years in six patients. Partial splenectomy was performed at

ages 6 to 13 years (patients 1, 4, 7, 8, 9), total splenectomy at ages 6 to 10 years (patients 2, 3, 5, 10).

Before treatment all patients had recurrent crises. Five (nos. 2, 4, 5, 6, 10) had had one or more episodes of pain in one or both hips, followed by radiographic signs of femoral head osteonecrosis and femoral head deformity. Four patients (nos. 3, 4, 5, 8) had suffered from crisis in the spine, and the remainder, in the pelvis and small and long bones. Four patients (nos. 2, 3, 4, 5) had pathological fractures at the site of crisis, one of the proximal femur, one of the distal femur and two of the spine.

Prior to beginning treatment, each patient underwent clinical and radiographic examination of the spine, pelvis and long bones. Blood was drawn for routine studies, enzyme assay of leukocyte acid,  $\beta$ -glucosidase and molecular testing. The effect of treatment was measured

according to the frequency of bone crises.

## RESULTS

During this entire period no pathological fractures occurred. The effect of enzyme replacement therapy on the frequency of bone crises is shown in Table 1. Five patients showed either no change with treatment or an increase or decrease by one episode. In one patient (no. 6) the number of crises decreased from six to one, in two patients (nos. 3, 10) crises decreased from three to one, and in one patient (no. 5) from three to zero. In only one patient (no. 8) was there a marked increase in crises, from one to four. Overall, there were eight bone crises in the first year, four in the second, two in the third, and one in the fifth.

Table 1. Clinical Data of Ten Patients

Patient No.	Sex	Age at Start of Treatment (yrs)	Duration of Treatment (mos)	Number of Bone Crises				Number of Months on this Therapy to Last Crisis	
				*Before Treatment	On Treatment				
					1-12 mos	1-2 yrs	2-3 yrs		3-4 yrs
1	F	14	38	1	0	0	1	0	36
2	F	20	29	1	0	1	0	-	12
3	F	17	31	3	0	0	1	-	30
4	F	8	33	2	1	1	0	-	15
5	M	19	26	3	0	0	0	-	0
6	F	6	54+	6	1	0	0	0	8
7	M	23	51	2	1	0	0	1	50
8	F	10	23	1	3	1	-	-	15
9	F	13	15	1	1	1	-	-	13
10	M	21	15	3	1	0	-	-	10

\* During the same number of months/years as length of treatment.

The low dose regimen was discontinued in patients who continued to have bone crises - in the second year, three patients (nos. 8, 9, 10), in the third year, three patients (nos. 2, 3, 4), and in the fourth year, one patient no. 1). Patient 5 was also placed on a higher dose regimen (60 IU/kg/month in four weekly fractions) in the third year of therapy because of the severity of his bone disease. Although he had no documented bone crises, he had continuous bone pain, probably related to his multiple fractures and orthopedic procedures. In the fifth year one of the two patients (no. 7) remaining on the original protocol was also given the higher dose after he suffered a bone crisis.

The average duration of the crises was two weeks. The clinical and radiologic manifestations were of equal severity before and during treatment. In no case was the hemoglobin below 9 gm/dl, the platelet count below 100,000/ $\mu$ l, or the white blood count below 2500/ $\mu$ l before treatment, since all but one of the patients had undergone splenic resection. However, after treatment, hemoglobin rose by 0.9 to 3.4 gm/dl in seven patients; two had no change, and one continued to have mild anemia. In one patient, the WBC and platelet count improved.

Liver size and spleen size (when present) tended to improve. However, measurement of the palpable edge of the liver and spleen provided only a very approximate evaluation of the change in size, since many of these patients had a transverse abdominal scar from partial or total splenectomy.

## DISCUSSION

A previous study that followed 46 patients at our center from 1960 to 1985 found that nine patients had 23 pathological fractures. Fifteen of these occurred two to twelve months after a bone crisis at the same site (4). These were all patients with severe juvenile onset type 1 disease. Eight out of the nine had undergone splenectomy between the ages of five and twelve years. The fractures occurred between the ages six to 18

years.

The present study shows that alglucerase replacement therapy for this subpopulation of patients with juvenile-onset type I Gaucher disease is completely effective in preventing fractures even though it is ineffective completely in preventing bone crises at a dosage regimen of 30 IU/kg/month in 13 fractions/month. Since 1991 we have only seen fractures in patients not yet receiving replacement therapy.

The assessment of patient response to alglucerase is multifactorial and difficult. Objective improvements in hematological parameters, weight, height, and sexual maturity may be related to other therapeutic measures, such as splenectomy. Earlier studies with high-dose low-frequency regimen (120 IU/kg/month) have shown evidence of bone repair. Serial bone biopsies showed a gradual return to a normal histological picture, with increased bone density and thickened cortices in a child after two years of treatment with 120 U/kg/body weight/month; x-ray films were normal after three-and-a-half years (15).

There are only occasional reports of bone crises in patients on a high-dose low-frequency regimen. In twelve patients followed for nine to twelve months, episodes of bone pain appeared to decrease before objective evidence of improvement was demonstrable on skeletal radiographs (10). Others reported that bone crises disappeared or dramatically decreased in number after three to four months (17). An 11-year-old patient had severe but diminishing bone crises in the first year of therapy (12), and a 23-year-old woman with multiple bone crises showed complete subsidence of skeletal symptoms in six months (18).

Beutler reported that three of four patients treated with the low-dose high-frequency regimen suffered no more pain attacks (19).

At the same time, Esplin and McPherson reported that both 30 and 60 IU/kg/month improved hematological findings but the bone lesions progressed, while 120 IU/kg/month improved the bone lesions (20).

At an intermediate dose of 60 IU/kg/month, avascular necrosis of the left humeral head developed in one patient 14 months after initiation of therapy (21). In another report, a patient on a low-dose, high frequency regimen suffered a crisis four months after treatment initiation (22). Finally, a Japanese boy was treated from age 5 years with 120 IU/kg/month for three months and then 30 IU/kg/month, which was gradually decreased to 20 and then 10 IU/kg/month over the next two years. He showed avascular necrosis of the right femoral head 24 months after treatment was started (23), but no further bone crises occurred in the subsequent 21 months, when the high 120 IU/kg/month dose was reinstated (24).

A group of 14 adults treated with the low dose/high frequency protocol who had suffered from chronic bone pain or repeated bone crises had disappearance of bone pains often within six months (8 patients) and significant improvement in bone pain with reduction in frequency and/or intensity of pain episodes (6 patients) (25). Four adults with type 1 disease have been reported who developed fractures during the first year of treatment (19,26). Three received 120 IU/kg/month and one 30 UI/kg/month. X-rays were available in three with documented pre-existing lesions. The patients were aged 38 year (19), 46 years (19) and 40 years (personal communication - Beutler) and 42 years (26).

Two children with type 3 disease also developed fractures on therapy. A 6-year-old patient with genotype L444P/L444P (1448C/1448C) developed a fracture in a shoulder lesion after three years of therapy (average) 60 IU/kg/month (10). The second non-Jewish child genotype 1504T (R463C) 84GG developed a fracture of his femoral neck aged 15 years, after seven months of 120 IU/kg/month (26). He had oculomotor findings (personal communication - Sidransky).

Although Gaucher patients with identical genotypes can exhibit considerable clinical

heterogeneity (27), the severest cases of type I disease occur in those who are compound heterozygotes for N370S and another mutation such as 84GG, L444P, and IVS2+1. Since the severity of Gaucher disease is associated with a young age at onset of hepatosplenomegaly, hypersplenism, splenectomy and crises (28), it is not surprising that pediatric departments will have more patients who are compound heterozygotes and fewer patients who are homozygous (N370S/N370S) and have the milder clinical phenotype (28).

At present 79% of the patients in our department are compound heterozygotes (29). Fifty-five percent of these patients had severe bone disease. Thus, we seem to have in our care an extremely seriously affected group of patients, in whom the lack of success in rapid elimination of crises is clearly demonstrated.

Even though splenectomy has been reported to be associated with an increase in bone crises and fractures (30) and partial splenectomy has not (31), there was no difference in outcome between patients who had undergone either operation.

It is intriguing to note that the only patient (no. 6) in whom this regimen was not discontinued and who can be considered a treatment success had not undergone any splenic resections. She was not untypical of the group, presenting at age 6.5 months with liver and spleen palpable 4 cm below the costal margin. The outcome in her case supports the opinion that splenic resection does not improve response to enzyme replacement therapy (21).

The greatest morbidity in Type 1 Gaucher disease has been due to bone crises. The two major problems were fractures and pain that may last up to several weeks (4-6) and may be difficult to control even with an intensive narcotic program (32). The problem of pain has now been overcome by the introduction of oral ambulatory high-dose prednisone therapy (33). This and the ability of alglucerase to prevent fractures has reduced the importance of bone crises.

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