CASE REPORT

Enzyme Replacement Therapy for Gaucher Disease: The Only Experience in Malaysia

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Summary

Gaucher Disease may now be treated with enzyme replacement therapy (ERT) or bone marrow transplantation (BMT). Both have their advantages and disadvantages. Results with BMT are curative when successful but limited by the scarcity of an appropriate donor. ERT offers very good relief of symptoms but treatment is lifelong and cost of treatment exorbitant. Patients in developing countries are particularly disadvantaged and management remains a dilemma for both doctor and patient.

Key Words: Gaucher Disease, Enzyme replacement therapy

Introduction

Gaucher Disease (GD) the most frequently occurring lysosomal storage disorder, is caused by a deficiency of the enzyme glucocerebrosidase (acid β-glucosidase) resulting in the accumulation of glucocerebroside in the monocyte-macrophage cells of the body[1]. This disease is subdivided into 3 phenotypes depending on the progression of disease and cerebral involvement. The commonest phenotype Type 1 is a chronic, non-neuronopathic disorder which nonetheless results in significant morbidity from fractures, bone pain, cytopaenia secondary to hypersplenism and eventual death from bleeding or infection. Type 2 disease is an acute neuronopathic form affecting infants from 3 - 4 months of age and becomes rapidly fatal by the age of 2 years. Type 3 has intermediate progression with severe visceral and variable central nervous system involvement. This autosomal recessive disorder affects all racial and ethnic groups and its incidence is estimated to be 1:50000 in the non-Jewish population. The gene for this lysosomal enzyme glucocerebrosidase is located at chromosome 1q21 and various point mutations and complex rearrangements have been described, making family studies and prenatal diagnoses possible.

The current treatment options for GD include enzyme replacement therapy (ERT) and bone marrow transplantation (BMT). Gene therapy remains experimental and has recently entered Phase I trials in America. Successful BMT offers a cure for GD[2] but only 30% of patients can expect to find a matched sibling donor. Worldwide, the number of patients who have undergone BMT remains low. In 1991 a replacement enzyme Alglucerase (CEREDASE) which targets

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macrophage receptors and isolated from human placentae, became commercially available. Regular infusions of this enzyme resulted in symptomatic relief, reversal of visceromegaly and improved growth.[3] However the cost of enzyme replacement therapy (ERT) is extremely high, making Alglucerase the "most expensive drug in the world". Even in developed countries where health insurance or the government pay for health care, there are problems of ceiling reimbursement and limited coverage for certain age groups. ERT often raises social and ethical issues in the treatment of rare genetic diseases. We report our experience in ERT for GD in a patient who is the first and currently only person to have received such treatment in Malaysia.

Case Report

MCTY born to healthy non-consanguineous Chinese parents in November 1988, developed progressive abdominal distention from the age of 5 months. Two years later in mid 1991 a diagnosis of Gaucher Disease was made in University Hospital, Kuala Lumpur when her gross hepatosplenomegaly led to a bone marrow examination which revealed the typical Gaucher cells. Over the ensuing three years she remained asymptomatic apart from the progressive hepatosplenomegaly at which point she was thought to have Type 1 disease. In 1991 a sibling was born and later tested in 1995 and found to be an incompatible bone marrow donor. At the same time a search for an unrelated cord blood unit found one which was partially matched. After weighing the risks and benefits, the patient's parents opted against the unrelated cord blood transplantation.

In September 1995, the patient's leucocytes were sent to Adelaide, Australia where her glucocerebrosidase level was confirmed to be low at 110 pmol/min/mg protein (normal 600 - 3200) and gene mutation studies showed the patient to be homozygous for the Gaucher mutation gene L444P. By this time, the patient aged 6 years began to complain of intermittent epistaxis and demonstrated developmental delay. Type 3 GD was then entertained. In January 1996 the patient was admitted for a significant episode of epistaxis. Physical examination showed a smooth kyphosis of the spine with her liver 3 cm and spleen 13 cm below the subcostal margins. Blood examination showed anaemia, thrombocytopaenia and a mild coagulopathy. (Table I)

On 2nd July 1996 at the age of 7 years 7 months the patient was started on enzyme replacement therapy after permission was obtained from the Malaysian Drug Control Authority. The enzyme Alglucerase (CEREDASE®) costing US$1480 per 400 unit vial, was imported from Massachusetts, USA and she received 400 units every fortnight (equivalent to 20 units /kg/dose). The enzyme was diluted in 100 mls of normal saline and infused intravenously over 2 hours. She did not develop any acute reactions or side effects. ERT continued until 23 May 1998 when her parents faced financial constraints.

The 22 months of ERT resulted in reduction of the patient's visceromegaly and improvement in her blood counts. Her splenomegaly decreased from 16 cm to 5.5 cm below the subcostal margin, with initial rapid response seen in the first six months of treatment. Splenic volume was objectively mesured with pre-ERT volume of 1592 cu.cm. decreasing to 856 cu.cm. post-ERT. The shrinkage of the liver was less remarkable from 3cm to 2 cm below the subcostal margin. There were no further episodes of epistaxis and her mild anaemia and thrombocytopaenia were corrected (Table I). She showed a decreased level of acid phosphatase from a peak level of 49.8 to 15.8 IU/L (Table I). In addition there was improved growth where height regained its previous centile (Figure 1).

Table I: Clinical Characteristics of Patient

Date	Apr '91	Mar '92	Apr '93	Aug '94	Jun '95	Jan '96	Jun '96	Dec '96	Jun '97	Dec '97	Mar '98	Dec '98	Jun '99	Dec '99	Jun '00	Dec '00
Enzyme Replacement							Started from 2 July 1996 till 23 May 1998									
Spleen size cm	7	9	10	NA	13	NA	16	9.5	9.0	9.0	6	5.5	NA	5	NA	7
Liver size cm	4	3	3	3	3	3	3	2	2	2	3	NA	NA	NA	NA	4
Hb g/dl	11.0	10.0	10.0	10.8	9.3	8.5	9.2	10.6	10.9	11.3	11.4	11.2	10.9	11.1	10.8	8.7
Platelets x 10^9/l	194	214	192	170	128	71	93	108	125	125	127	154	136	147	139	99
WBC x 10^9/l	8.2	6.5	6.0	6.7	4.3	3.1	4.7	4.9	5.4	5.7	6.4	5.3	5.6	4.7	4.5	1.2
Neutrophil %	48	48	69	54	28	34	35	41	46	45						30
Lymphocyte %	48	46	26	41	68	58	56	48	42	44						57
Acid Phosphatase IU/l	28						32.8	49.8	37.9	15.8						
PT Seconds	1.3					1.16			1.25							
PTT (patient/ Normal) Seconds	47.7 / 38.4					51.5 / 33.9			49.9 / 32							

However 2 years after stopping ERT, the patient's symptoms recurred. In addition more neurological symptoms relating to behavioural and learning difficulties surfaced. In October 2000, the patient developed recurrent seizures.

Discussion

Our patient suffered progressive hepatosplenomegaly, haematologic abnormalities, slowing of growth and neurological symptoms. With time what was thought to be Type 1 Gaucher Disease (GD) became Type 3 disease. Unlike some other Malaysian patients with GD who may not be able to afford any form of treatment, this patient had some options.

Enzyme Replacement Therapy (ERT) using the human placentae derived enzyme Alglucerase (CEREDASE) was started for patients with Type 1 GD in 1991 in the USA[4]. Numerous reports of its effects and patient response subsequently followed. Patients had symptomatic relief from bone pains, impressive reductions in visceromegaly and amelioraton of cytopaenias. While there were no doubts about its efficacy, the extreme high cost associated with its use led to different dosing regimes[5]. The most common regime advocates a dose of 30 - 60 units/kg/month given every fortnight. Our patient was given this regime and showed satisfactory response. The size of her spleen reduced dramatically. Correction of her

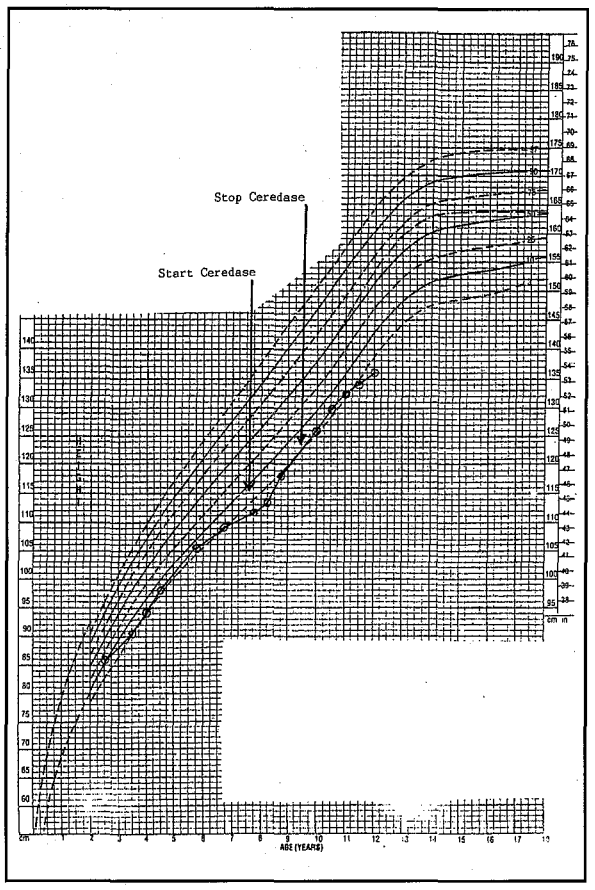

Fig I: Growth Chart for Height

thrombocytopaenia was reflected in the cessation of epistaxis. Her height which had decreased below the 3rd centile for age regained its previous centile while the patient was on ERT (Figure 1). There is some evidence that a higher dose reaching 120 - 480 units/kg/month may stop or at least retard neurological deterioration in Type 3 disease. However, with the exorbitant cost of the drug, there is no opportunity to test this out in our patient. In an effort to reduce cost, a low dose high frequency regime has been tried but seems to afford less bone and skeletal responses[5]. In 1995 a recombinant enzyme with similar efficacy imiglucerase (CEREZYME) became available but cost has remained unchanged.

ERT is necessarily life long and the cost is unlikely to decrease in the near future. A 400 unit vial of CEREDASE cost US$1480 and in total our patient spent RM208088 for 22 months of treatment. This is ten times the cost of a paediatric bone marrow transplantation in our institution. Without any reimbursement schemes, it is impossible to expect any family to finance ERT. Within 2 years of stopping ERT the patient's problems have all recurred i.e. enlarging spleen, cytopaenia and slowing of growth (Table I and Figure 1). A number of similarly affected children in Malaysia have no treatment at all. These children may expect transfusions for anaemia and thrombocytopaenia and possibly splenectomy when their hypersplenism becomes unmanageable.

Bone Marrow Transplantation (BMT) offers cure for GD with early resolution of visceromegaly and haematological abnormalities while improvement in bone marrow and skeletal tissues is delayed[2]. Reported cases of BMT have used matched sibling or phenotypically matched parental donors. Generally where there is a matched sibling donor, BMT should be the treatment of choice. Obstacles to successful transplantation are graft-versus-host disease, graft failure and regimen related toxicities but improved supportive care and better immuno-suppression have decreased the mortality and morbidity seen with this procedure. Umbilical cord blood has been proposed as an equivalent and sometimes better source of stem cells for transplantation particularly in paediatric patients. Cord blood transplanatation (CBT) requires less stringency in human leucocyte antigen (HLA) matching and compared with unrelated matched BMT, a lower incidence of graft-versus-host disease has been reported even with 2 or 3 antigen mismatches. The cost of a BMT or CBT would be less than 50% of the cost of ERT for 1 year. Although our patient does not have a matched sibling donor, the availability of a 5 out of 6 antigen matched cord blood unit offers a reasonably good chance

of a cure. However in her case, her parents were not prepared to take the risks associated with transplantation, thus denying her the chance of a cure. Her long-term prognosis is likely to be poor.

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