RESEARCH PAPER

Outcome of Gaucher Disease in India: Lessons from Prevalent Diagnostic and Therapeutic Practices

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Objectives: To study disease severity and response to enzyme replacement therapy in Gaucher disease.

Methods: Updated data was captured from records of 37 patients (35 reported previously) with confirmed diagnosis of Gaucher disease from January 1995 through December 2011 (31, 83.8 %) and prospectively from January 2012 through June 2013 (6, 16.2 %). Severity of manifestations was determined by Gaucher disease Severity Score Index. Response to enzyme replacement therapy was assessed in terms of attainment of therapeutic goals.

Results: Moderate to severe manifestations (domain score of > 2) were observed in treated patients at baseline (83%, 58%, 66% and 25% for anemia, thrombocytopenia, hepatomegaly and leucopenia, respectively and 100% for splenomegaly and elevated plasma chitotriosidase). None of the 11 patients treated with synthetic enzyme (average annual dose 23 to 53 units/kg) attained all therapeutic goals in the recommended time frame, particularly the visceral, skeletal and growth domains.

Conclusions: Early onset of moderate to severe disease in Indian patients mandates early therapy with optimum doses to ensure attainment of all recommended therapeutic goals.

Keywords: *Glucocerebrosidase deficiency, GBA 1 gene, lysosomal storage disease.*

Gaucher disease in populations of Asian ancestry is a severe, rapidly progressive phenotype with younger age at onset, severe hematological, visceral and bone involvement, higher frequency of neuronopathic disease and p. Leu483Pro as the most frequent *GBA 1* gene allele [1]. Enzyme replacement therapy (ERT) is not widely available in India. Multicentric data is available on the phenotypic spectrum and response to enzyme replacement therapy in 25 individuals with Gaucher disease in India [2]. However, data on disease severity, dosing, bone disease and genotype was incomplete. This study was therefore performed to analyze disease severity and response to ERT at a single center in Western India.

METHODS

The study was approved by the Institutional Ethics Committee of our institute. Records of patients with confirmed diagnosis of Gaucher disease (by estimation of β-glucocerebrosidase activity and/or identification of pathogenic mutations and/or histopathological evidence of Gaucher cells) were retrospectively reviewed from January 1995 through December 2011 (*n* = 31, 83.8 %) and six patients (16.2%) were prospectively enrolled from January 2012 through June 2013. Of these, 35

cases constituted a subset of lysosomal storage disorders analyzed previously for diagnostic time frame and genotype [3].

Parameters analyzed were age at diagnosis and initiation of ERT. Severity of manifestations were graded by Gaucher disease Severity Score Index (GauSSI) [4]. In those receiving ERT, dose and duration was determined for each case. Therapeutic response was analyzed according to published therapeutic goals [5].

RESULTS

Of the 37 confirmed cases (22 males), phenotypic classification was possible in 22 cases: 45.4% had type 1 disease and 41% had type 3 disease. The most frequent *GBA 1* gene allele was p. Leu483Pro in 10 (62.5%) cases (8 homozygous, 2 heterozygous).

The average age (range) at onset of symptoms, presentation to our center and diagnosis was 28 (1-150), 56 (3.5-228) and 56 (4-229) months, respectively. The average delay in diagnosis from the initial symptoms was 30 months (range 1-154). The severity of manifestations, are described in **Table I**. Only hematologic and biomarker (plasma chitotriosidase) domains could be scored as due to financial constraints, very few patients

TABLE I CLINICAL CHARACTERISTICS AND SEVERITY SCORE WITH GauSSI FOR HEMATOLOGIC AND BIOMARKER DOMAINS IN STUDY SUBJECTS (*N*=37)

Manifestations	On ERT (n = 12)	Untreated (n = 25)	Total (%)
Anemia	11	20	31 (83.7)
0 (>12)	1	5	6 (16)
1 (10-12)	1	2	3 (8)
2 (8-9.9)	3	8	11 (30)
3 (< 8)	7	10	17 (46)
Thrombocytopenia	9	12	21 (56.7)
0 (>150)	3	13	16 (44)
1 (101-150)	2	3	5 (13)
2 (60-100)	2	3	5 (13)
3 (<60)	5	6	11 (30)
Leucopenia	5	7	12 (32.4)
0 (>4)	7	18	25 (67.5)
1 (2.5-4)	2	1	3 (8)
2 (<2.5)	2	2	4 (11)
3 (<1.9)	1	4	5 (13.5)
Blood transfusion	7	5	12 (32.4)
Bleeding/bruises/petechiae	6	0	6 (16.2)
High plasma chitotriosidase*	11	7	18 (85.7)
0 (<600)	0	0	0
1 (600-4000)	0	1	1 (5.5)
2 (4001-15000)	4	4	8 (44.4)
3 (>15000)	7	2	9 (50)

Total 21, with 9 untreated.

had imaging for bone disease and organ volume ascertainment and evaluation of lung domain.

ERT was initiated in 12 cases. Before commencing ERT, all 12 cases had splenomegaly and hepatomegaly whereas stunting (height <3rd centile, NCHS chart) was noted in 10 (83.3 %) and osteopenia (DEXA Z score -1 to -2.5) in 9 (75%). Three (25%) had undergone splenectomy. Baseline liver volume in one patient was <1.25 times normal, four each had moderate hepatomegaly (1.25-2.5 times normal) and severe hepatomegaly (>2.5 times normal) and in three individuals baseline liver volume was not available. The average liver volume was 2.27 times normal (range of 1.06-4). Nine individuals with an intact spleen had severe splenomegaly (volume > 15 times normal, average 40.2 times normal, range: 20.7-67). The average (range) age at initiation and duration of ERT was 85 (17-140) months and 55 (1-144) months, respectively. Average annual dose ranged from 23-53Units/kg and

varied every year. Response to enzyme replacement was prospectively analyzed in 11 out of 12 cases (7 males; 7 with type 1 disease and 4 with type 3). One 10 year old with advanced disease died due to intracranial hemorrhage after the first infusion of ERT. The response to ERT is presented in *Table* **II**.

DISCUSSION

The broad phenotypic spectrum of Gaucher disease and wide variation in severity makes treatment with ERT a challenge. Acknowledging these aspects has resulted in adoption of individualized dose regimen [6,7].

A key determinant of the initial treatment dose is disease severity, rate of progress, nature of organ involvement and impact of disease manifestation on quality of life [6,7]. This stratifies patients to high or low risk groups [7]. Children are categorized as high-risk on the basis of various clinical and laboratory parameters [6,7]. A dose of 60 Units/kg every two weeks has been recommended to treat high-risk children and as a minimum dose for children with type 3 phenotype [7,8].

We found that Indian children have severe disease based on the following observations: early age of onset (average of 28 months), objectively graded moderate to severe manifestations of splenomegaly, hepatomegaly, anemia and thrombocytopenia corroborated by extremely elevated plasma chitotriosidase levels (indicating a high disease burden) [9], and high proportion of the severe genotype (p.Leu483Pro) (representing severe manifestations and neuronopathic disease) [8]. The severe manifestations could partly be attributed to the diagnostic lag (average of 30 months) in our study.

Thus majority of our cohort would be candidates for receiving a dose of 60 Units/kg every two weeks as they have multiple high risk criteria. Due to supply constraints, our children received low doses that varied every year. Despite receiving dose of <60 Units/kg, early response with hematological reconstitution by the first year of therapy was adequate. However, the visceral and skeletal response digressed from the recommended targets. Only 50% and 25% of ERT recipients achieved the target reduction in liver and spleen volume, respectively by the first year of therapy. Skeletal response was likewise suboptimal with only 22% showing improvement in BMD and 30% achieving normal height by 3 years. As visceral and skeletal response is dose-dependent and determined by age at initiation of ERT; late initiation, high disease burden and low doses was the most likely cause for sub-optimum visceral and skeletal response [10-12].

A publication describing collective results of five

TABLE II RESPONSE TO ENZYME REPLACEMENT THERAPY IN TERMS OF ACHIEVEMENT OF THERAPEUTIC GOALS WITHIN THE RECOMMENDED TIME-FRAME

Therapeutic goal	Time to achieve goal	Before ERT, no(%)	After ERT, no(%)
Hemoglobin			
• Increase to >11 g/dL	1 to 2 years	2(18.1)*	7/10(70)#
• Received transfusions		7 (63.6)	0
Platelet count			
• Increase to prevent bleeding	1st year	6 (54.5)	10 (100)
• Avoid splenectomy: Splenectomy		2 (18.1)	0
• Splenectomized patients: Normalization	1st year	2/2 (100)	2/2 (100)
• Intact spleen, moderate thrombocytopenia:$		4/9 (44.4%)	
- Increase by 1.5 to 2.0 fold	1st year		4/4 (100)
- Approach low normal (Normal> 150000)	2nd year		3/4 (75)
Intact spleen, severe thrombocytopenia‡:		3/9 (33.3)	
- Increase by 1.5 fold	1st year		2/2#
- Continue to increase	Years 2-5, doubling by year 2		2/2#
*Liver volume reduction^*			
• By 20% to 30% 1st year			5/10 (50)#
• By 30-40% Year 3 – 5			4/7 (57.1)
*Spleen volume reduction^*			
• By 30% to 50%	1st year		2/8 (25)#
• By 50% to 60%	Year 2-5		3/6 (50)
Bone			
• Lessen or eliminate bone pains	1- 2 years	2	0
• Prevent bone crisis		2	0
• Prevent osteonecrosis and subchondral joint collapse	2 years	2	0
• Improve BMD; increase cortical and trabecular BMD		3**	2/9 (22)##
Growth			
• Normal height	3 years	1(9)	3/10 (30)#

*Splenectomy prior to commencing ERT; #Duration of ERT was <1 year in one patient; $platelet count 60000-120000, platelet count‡: 60000, ^n=9; **Baseline DEXA spine Z score < -1; ##Follow-up DEXA spine Z score >-1.

Indian centers has shown significant hematological and visceral response and improved weight and height [2]. However, parameters that were not addressed in this early publication were dose of ERT, objective severity of disease and response in terms of prescribed therapeutic goals. Additionally, as skeletal and growth response are only observed after the third year of treatment [5,8], the relatively shorter duration of therapy (average of 2.5 years in eight out of 22 patients completing more than one year therapy) did not permit effective conclusions. Thus our study contributes to the experience of treating Gaucher disease in India by documenting long-term data against established therapeutic goals.

A limitation of our study was reliance on retrospective data due to which clinical information was incompletely captured, evaluations were partial and patients were lost to follow-up. The other limitation was lack of complete systemic assessment of solid organs, lungs, heart and skeleton by imaging due to financial constraints as all expenses were out-of-pocket. In conclusion, severe disease phenotype and higher proportion of type 3 disease in Indian children necessitates ERT in higher doses along with cautious dose tapering for long term management if optimum response in all disease domains is to be a reality. As ethnic/geographic background of a Gaucher disease population may be a consideration for optimum dosing [7], our study has important therapeutic ramifications. Such phenotype and risk categorization of Indian children along with comprehensive pre-treatment evaluation of organ involvement and disease burden

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WHAT THIS STUDY ADDS?

• Severe phenotype of Gaucher disease in Indian children stratifies them to the high-risk category.

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would determine whether the therapeutic promise of ERT in India is realized in its entirety.

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