Original Articles

CLINICAL AND ENZYME STUDIES IN GAUCHER DISEASE

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Objective: *To study the clinical and biochemical spectrum of Gaudier disease.* ***Design:*** *Assay of β glucosidase enzyme in leucocytes in patients with splenomegaly, and in chorionic villi for prenatal diagnosis.* ***Setting:*** *Hospital-based.* ***Subjects:*** *Of 13 cases of Gaudier disease, aged 1-6 years, 9 were identified at Delhi and 4 at Bombay.* ***Results:*** *The enzyme β-glucosidase was 0.65 nmol/h/mg of protein or less in all the cases in Delhi, and 2.5 nmol/h/mg of protein or less in Bombay. All cases except one belonged to type 1 (hepatosplenomegaly), while one case was of type 2 (neuronopathic). Prenatal diagnosis was carried out in one family and the fetus was found to be affected.* ***Conclusion:*** *In children with hepatosplenomegaly and increased acid phosphatase, assay of β-glucosidase enzyme confirms the diagnosis of Gaudier disease. Diagnosis of the disease is important because enzyme replacement therapy is available and prenatal diagnosis is possible.*

Key words: *Gaudier disease, p-glucosidase in leucocytes, Prenatal diagnosis.*

GAUCHER disease is caused by the deficiency of cerebroside beta glucosidase which results in the storage of glucocerebroside in the lysosomes of reticuloendothelial cells mainly of spleen, liver and bone marrow(l). Clinically three types are recognized(2). Type 1 is characterized by hepatosplenomegaly and skeletal involvement; type 2 by acute severe neurological involvement; and type 3 by slowly progressive neurological involvement. We report 13 cases of Gaucher disease identified in Delhi and Bombay by enzyme assay in leucocytes. Fetal diagnosis was carried out in one woman at risk.

Subjects and Methods

All the patients had **a** thorough clinical evaluation. For assay of glucocerebrosidase, leucocytes were separated from the blood, collected in EDTA tube and the enzyme activity was determined fluorometrically as described elsewhere(3), using substrate 5 m M 4 methyl umbelliferyl-B-D-glucopyrnoside, in 0.1M acetate buffer pH 4.4 containing 0.2% (w/ v) sodium tauroglycocholate. In Bombay, the enzyme activity was estimated fluorometrically by using the same substrate in 0.2 M sodium citrate phosphate buffer pH 5.4.

Results

Thirteen children belonging to twelve families were identified to have Gaucher's disease, based on their clinical features arid beta glucocerebrosidase activity in leucocytes. Nine were diagnosed at Delhi and four at Bombay. Leucocyte (3-glucosi-

dase enzyme activity in the homozygotes and heterozygotes is shown in *Table I.*

At Delhi, the enzyme activity in homozygotes varied from zero to 11% of the normal control value, whereas in the carrier parents it varied from 17-53.8% of the normal mean control value. In Bombay, the enzyme activity in homozygotes varied from 0.95-2.5 nmol/h/mg protein. The enzyme activities at the two centers differed due to variable assay conditions. Based on clinical features, 12 cases were of type 1 disease and one (case 7) of type 2 disease.

Gaudier Disease Type 1

Of the 12 cases, 7 were females and 5 males. Age at diagnosis varied from 1-6 years (10 cases were between 1-2 years). The disease presented in all cases with failure to thrive and abdominal distension. Size of the liver varied from 3-10 cm and that of spleen from 6-27 cm. The spleen was invariably much more enlarged than the liver. All the patients were anemic. The skeletal manifestations were not seen in any of the cases. Acid phosphatase was markedly elevated in all cases (7-12 folds). The involvement of central nervous system was not observed although mild delay in motor milestones was noted in 4 cases probably due to massive splenomegaly and abdominal distension resulting in reduced mobility.

TABLE I—*Leucocyte beta Glucosidase Activity (nmol/h/mg protein)*

Case No.	Ethnic group	State of origin	Patient	Father	Mother
Delhi cases*					
1.	Sikh	Punjab	0	1.22	1.34
2.+	Sikh	Punjab	0.54	1.22	1.34
3.	Hindu	Orissa	0.45	1.16	1.0
4.	Hindu	Andhra Pradesh	0.63	1.01	1.15
5.	Hindu	U.P.	0.58	1.57	2.7
6.	Hindu	U.P.	0.65	3.15	1.3
7.	Muslim	Kashmir	0.45	ND	ND
8.	Hindu	Rajasthan	0.34	2.3	2.05
9.	Muslim	Rajasthan	0.55	ND	ND
Bombay cases**					
10.	Hindu	Maharashtra	1.2	7.8	8.6
11.	Muslim	Maharashtra	2.5	ND	ND
12.	Jain	Maharashtra	1.1	ND	ND
13.	Hindu	Maharashtra	0.95	ND	ND

ND = Not done
* Enzyme activity in normal controls (n=10) = 5.86±1.5 nmol/h/mg protein (range 3.8-8.7).
** Enzyme activity in normal subjects ranged from 5-22 nmol/h/mg protein.
+ Brother of case 1.

Gancher Disease Type 2

A 2-year-girl (case 7) was the product of a consanguineous Muslim couple from Kashmir. She had repeated chest infections, regression of milestones and seizures. The girl had noisy breathing emanating from the throat. She had mild ptosis and squint but the fundus was normal. Liver was palpable 2 cm and spleen up to 6 cm below the costal margin. There were no coarse facial features. β−glucosidase activity was 0.45 nmol/h/mg of protein (7.6% of the normal mean control value). Her elder sister with similar complaints had died at the age of 1.6 years.

Prenatal diagnosis was done in the next pregnancy of the mother of case 7. The β glucosidase activity in a sample of chorionic villi obtained at 10 weeks of gestation was 10.9 nmol/h/mg protein, which was markedly deficient as compared to that in two control chorionic villus samples (112 and 114 nmol/h/mg). In the chorionic villus samples, two more enzymes, *viz*., β−galactosidase and alpha fucosidase were also estimated and found to be normal. This indicated that the fetus was affected with Gaucher disease. The parents opted to abort the fetus.

Discussion

Gaucher disease is an autosomal recessive disorder, the gene for which is located on chromosome 1. Of the three types of Gaucher disease, type 1 is the commonest(2). In the present study, 12 of 13 cases were of type 1. Gaucher cells were present in the bone marrow in all the cases. Serum acid phosphatase was also high in all the cases.

A quantitative estimation of beta glucosidase in leucocytes is required for confirmation of the diagnosis. In the present study, the mean value of β-glucosidase in homozygotes was 7.9% of control value, with a range of 0-11%. β-glucosidase activity in leucocytes of heterozygote parents ranged from 17-53.8% of the control value in normals.

Bone marrow transplantation (BMT) provides a permanent cure when successful(4). BMT can be carried out in India in Vellore, Bombay and Delhi. In recent years, enzyme replacement for type 1 Gaucher disease has emerged as effective therapy. Both the natural enzyme obtained from the placenta, and the recombinant enzyme have been used for therapy with excellent response (5-8). A review of the reported studies suggests that in Indian children with type 1 disease, alglucerase enzyme treatment at low dose (15 units/kg/month) is preferable and would improve the quality of life of these patients.

We suggest that children with hepatosplenomegaly where diagnosis of Gaucher disease is suspected, should have acid phosphatase estimated in blood, while the bone marrow should be examined for the presence of Gaucher cells. Diagnosis should be confirmed by β-glucosidase assay. Low dose enzyme replacement may be instituted if the parents can afford the therapy. The parents should be counselled about the 25% risk of recurrence and the availability of prenatal diagnosis by enzymatic assay in chorionic villi sample at 10-12 wk of gestation or amniotic cell culture at 15-18 wk. The authors have formed a parents support group for Gaucher disease, which would subsidize 50% of the cost of enzyme therapy and would be happy to provide more information to those who require it.

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NOTES AND NEWS

B.C. ROY NATIONAL AWARDS, 1996

Dr. S.P. Srivastava, Professor and Head, Upgraded Department of Pediatrics, Patna Medical College, Patna and Dr. Bijon K. Chakraborty are the recipients of B.C. Roy National Award for the year 1995 in the category of Eminent Medical Teacher. Heartiest congratulations from the Pediatric fraternity.

VIITH MAHARASHTRA STATE IAP CONFERENCE

This event will be held at Mumbai from 10-13th October, 1996 under the auspices of Mumbai Branch of IAP. The main conference will be held at Tata Memorial Hospital, Mumbai on 12th and 13th October, 1996. There will be 8 Preconference Workshops to be held concurrently on 10th and 11th October, 1996, one at each major medical institute. For further details please contact: Dr. M.R. Lokeshwar, Organizing Chairman or Dr! Nitin Shah, Organizing Secretary, Kashyap Nursing Home, 3rd Floor, Imperial Mahal, Khodadad Circle, Dadar T.T., Mumbai-400 014, Tel. 4128020 Fax: 00-91-22-4145056-Attn. Dr. M.R. Lokeshwar.