

Pulmonary function abnormalities in type I Gaucher disease

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Pulmonary function abnormalities in Type I Gaucher Disease. E. Kerem, D. Elstein, A. Abrahamov, Y. Bar Ziv, I. Hadas-Halpern, E. Melzer, C. Cahan, D. Branski, A. Zimran. ©ERS Journals Ltd 1996.

ABSTRACT: The purpose of this study was to determine the prevalence of pulmonary function and radiographic abnormalities among patients with type I Gaucher's disease, and to analyse the relationship between the pulmonary involvement and genotype and clinical severity score.

All patients attending the Gaucher clinic at the Shaare Zedek Medical Center, Jerusalem, Israel, during the years 1992–1993 were prospectively evaluated. Each patient had pulmonary function tests, chest radiography, clinical assessment in terms of degree of organ involvement, and genotype analysis.

Of the 95 patients included in the study (mean±SD age 29±15 yrs), 68% had some pulmonary function abnormalities, most commonly a reduced FRC and transfer coefficient for carbon monoxide (K_{CO}), found in 45% and in 42% of the patients respectively. Total lung capacity (TLC) was reduced in 22% of the patients and forced expiratory flows in approximately one third of the patients. Signs of air-trapping (elevated residual volume (RV) or RV/TLC) were seen in 18% of the patients. Males had a higher incidence of reduced expiratory flow than females, (forced expiratory volume in one second (FEV₁) was reduced in 36% of males vs 5% of females). Chest radiographic abnormalities were found in 17% of the patients, although only 4% had severe changes. Patients with abnormal pulmonary function had a significantly higher severity score index than those with normal pulmonary function tests. There was no association between abnormal pulmonary function and genotype or age.

In conclusion, abnormal pulmonary function is common among type I Gaucher patients. Pulmonary function tests show airways obstruction, with reduced expiratory flows, reduction in lung volumes and alveolar-capillary diffusion abnormality. The rate of progression and the clinical significance need to be determined.

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Gaucher disease is the most prevalent lysosomal storage disease. It is inherited as an autosomal recessive disorder, resulting in an impaired activity of glucocerebrosidase, which causes an accumulation of the sphingolipid glucosylceramide in the cells of the reticulo-endothelial system ("Gaucher cells"). This abnormal deposition occurs primarily in the bone marrow, spleen and liver, although typical Gaucher cells have also been noted in other organs [1]. Classically, Gaucher's disease is divided into three forms based on the presence and severity of the neurological component [2, 3]. However, considerable variability, even within each category, has been documented. Type I Gaucher's disease is the non-neuronopathic form; many patients are asymptomatic or very mildly affected. The remainder of patients may show mild to severe visceral manifestations, including hepatosplenomegaly, thrombocytopenia, bone lesions and occasionally other organ involvement. There is a predilection for type I disease in the Ashkenazi Jewish population. Type II and type III Gaucher's disease are relatively rare and both are marked

by a fulminant neuronopathic course, which portends a fatal outcome in type II, and more heterogeneous course in type III. Pulmonary involvement is generally noted in both of these latter forms, especially in conjunction with liver deterioration. Pneumonia (often aspiration) and/or respiratory failure are the most common causes of death [3].

Pulmonary involvement is considered to be rare in type I Gaucher's disease [1]. Sporadic case reports have demonstrated the occurrence of increased pulmonary infections, pulmonary hypertension, bilateral interstitial lung disease, or hypoxaemia due to intrapulmonary arterial-venous shunts in patients with severe hepatic disease [4–14]. However, most of the reported cases contain children whose early age of diagnosis and onset of disease symptoms may, in themselves, indicate a more severe form of the disease. Lung involvement may be the direct result of Gaucher cell infiltration, secondary to extensive hepatic disease, or to mechanical compression due to hepatosplenomegaly [15]. In a short report by

LEE and YOUSEM [16], more than one third of autopsied Gaucher patients showed significant abnormalities in the lung. Their description of the pulmonary lesions is consistent with other anecdotal reports [9, 12, 13] of diffuse reticulonodular infiltrate or miliary pattern upon chest radiographs in several patients with diverse clinical patterns. Nonetheless, the extent of lung involvement as part of the clinical presentation of type I Gaucher patients with mild-to-moderate disease has not been documented.

The purpose of this study was to ascertain the extent of pulmonary function and radiographic abnormalities in patients with type I Gaucher's disease and to analyze the relationship between pulmonary involvement, and genotype and clinical severity of Gaucher's disease.

Patients and methods

All patients, diagnosed by enzyme assay of leucocyte β -glucosidase, who presented to the Gaucher Clinic at Shaare Zedek Medical Center during the 2 year period of 1992–1993, were prospectively included in this study. Pulmonary function studies were performed in all patients above 6 yrs of age, who were able to perform the tests. They included standard spirometry, lung volumes using the nitrogen wash-out technique, carbon monoxide transfer coefficient corrected for lung volume and haemoglobin (K_{CO}). Forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), peak expiratory flow rate (PEFR), total lung capacity (TLC), functional residual capacity (FRC), forced expiratory flow over the middle half of the vital capacity (FEF_{25-75}), forced expiratory flow at 25, 50 and 75% of vital capacity (FEF_{25} , FEF_{50} , FEF_{75} respectively), residual volume (RV) and K_{CO} , expressed as a percentage of predicted values for height and sex, computed with previously described standardized equations [17, 18].

For calculations of the incidence of abnormal pulmonary function, values were regarded as abnormal if they were below 80% predicted for FEV_1 , FVC, TLC, FRC and K_{CO} , and below 70% predicted for FEF_{25-75} , FEF_{25} , FEF_{50} , and FEF_{75} . RV was regarded as abnormal above 120% predicted, and RV/TLC value was regarded abnormal above 35%. When comparing the clinical differences between patients with normal *versus* abnormal pulmonary function, a slightly stricter set of cut-off points was used; abnormal pulmonary function was considered below 70% predicted value for FEV_1 , FVC, PEFR, TLC, FRC and K_{CO} ; below 65% predicted value for FEF_{25-75} , FEF_{25} , FEF_{50} , FEF_{75} ; above 130% predicted value for RV; and above 40% predicted value for RV/TLC. Thus, the stricter criteria in describing abnormal pulmonary function was used in order to identify only those patients whose abnormality might be clinically significant.

Chest radiographs were reviewed by two radiologists (YBZ and IHH), who were unaware of the patients' status. Interstitial lung disease was graded according to the following criteria: grade 0 for normal films; grade 1 for minimal diffuse reticulonodular changes; and grade 2

for prominent reticulonodular changes. All other abnormalities when seen, were recorded.

The relative severity of Gaucher's disease was assessed in terms of the degree of organ involvement and the age at diagnosis. A numerical value, the severity score index (SSI): 0–10 indicating few overt signs and late recognition of the disease; 11–20 indicating moderate signs; and >20 indicative of considerable visceral involvement and early diagnosis of the disease [19]; and the same index without the numerical weight of the age of diagnosis (SSNA) [20], were assigned to each patient in order to standardize description of the clinical profile. Pulmonary function is not included in the severity score indices.

Abdominal ultrasound studies were performed to assess the measurements and parenchymal texture of the liver. The liver volume index [21] was used to correlate between the liver size and the pulmonary function abnormalities. The liver volume index, which is directly related to the product of the three maximal dimensions: anterior-posterior, longitudinal, and transverse (ultrasonic imaging (USI)), has been shown to correlate closely with quantitative measurements of organ size carried out by magnetic resonance imaging [21].

Mutation analysis was performed on high molecular weight deoxyribonucleic acid (DNA) extracted from peripheral white blood cells using standard methods. Nine mutations of the glucocerebrosidase gene, accounting for approximately 90% of mutated alleles in the Ashkenazi Jewish population and approximately 73% of the mutated alleles in the non-Jewish population, were screened as described previously [22].

Statistical analysis

For variables which were normally distributed, such as age and weight, Student's t-test was performed. Categorical data, such as sex or type of mutation, were compared using chi-squared analysis. For variables which were not normally distributed (SSI, SSNA, chest radiographic score), the nonparametric test (Mann-Whitney) was performed. Analysis of variance with covariates was used to isolate gender differences in comparisons of differences between groups with normal *versus* abnormal pulmonary function tests (PFT). Multiple regression analysis was used to evaluate the correlation of pulmonary function values and clinical parameters. Pearson Product Moment Correlation was used for correlation between liver volume index and pulmonary function. Data are presented as mean value \pm SD, unless otherwise indicated.

Results

Of the 112 Gaucher patients followed in our Gaucher clinic between the years 1992–1993, 11 children under the age of 6 yrs were excluded, as were six other patients who did not perform PFT or for whom data were unavailable. Thus, our study group included 95 patients, of whom 59 (62%) were females. The mean \pm SD age was 29 ± 15

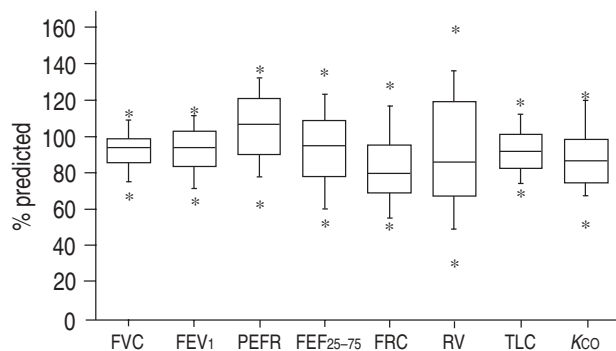


Fig. 1. – Box plots presentation of pulmonary function values of Gaucher patients (n=95). The box represents the middle 50% of the data. The horizontal line inside the box is the median value. The upper and lower ends of the box show the upper and lower quartiles. The vertical lines show the 95% range. Asterisks represent points outside this range. FVC: forced vital capacity; FEV1: forced expiratory volume in one second; PEFR: peak expiratory flow rate; FEF₂₅₋₇₅: forced expiratory flow over the middle half of the vital capacity; FRC: functional residual capacity; RV: residual volume; TLC: total lung capacity; K_{co}: transfer factor of the lungs for carbon monoxide.

ys (range 7–66 years), the mean SSI was 10.6 ± 6.4 , and SSNA 8.0 ± 5.4 .

Figure 1 shows the distribution of the results of the pulmonary function tests among the patients, and table 1 shows the proportion and values of abnormal pulmonary function parameters. The most common pulmonary function abnormality was reduced FRC found in 45% of the patients followed by reduced diffusion capacity, as measured by K_{co}, found in 42% of the patients (table 1). Lung volume, as measured by TLC and FVC was reduced

Table 1. – Proportions and values of abnormal pulmonary function test (PFT) variables among Gaucher patients and their clinical severity score (n=95)

	Abnormal %	Pulmonary function % pred	SSI	SSNA
FVC	17	63 ± 13	14.9 ± 8.1	11.8 ± 6.9
FEV ₁	17	66 ± 12	16.7 ± 7.0	13.1 ± 5.8
PEFR	11	64 ± 11	13.5 ± 6.0	11.7 ± 5.4
FEF ₂₅	18	57 ± 12	12.6 ± 6.7	9.5 ± 5.7
FEF ₅₀	31	54 ± 14	12.9 ± 6.2	10.6 ± 5.7
FEF ₇₅	27	51 ± 15	13.6 ± 6.8	11.5 ± 5.9
FEF ₂₅₋₇₅	19	56 ± 13	12.8 ± 6.6	10.3 ± 5.9
FRC	45	66 ± 14	11.9 ± 7.0	9.1 ± 5.9
RV	18	145 ± 21	13.4 ± 7.1	1.0 ± 6.0
TLC	22	71 ± 9	13.9 ± 7.8	10.3 ± 6.7
RV/TLC	16	40 ± 4	12.6 ± 8.4	10.1 ± 6.8
K _{co}	42	67 ± 16	11.8 ± 6.9	9.0 ± 5.6

Values are presented as mean \pm sd. FVC: forced vital capacity; FEV₁: forced expiratory volume in one second; PEFR: peak expiratory flow rate; FEF₂₅, FEF₅₀, FEF₇₅: forced expiratory flow at 25, 50 and 75% of vital capacity, respectively; FEF₂₅₋₇₅: forced expiratory flow over the middle half of the vital capacity; FRC: functional residual capacity; RV: residual volume; TLC: total lung capacity; K_{co}: transfer factor of the lungs for carbon monoxide; SSI: severity score index; SSNA: SSI without the numerical weight of the age of diagnosis; % pred: percentage of predicted value.

in approximately one fifth of the patients. Although most of the patients had reduced RV and FRC values, approximately 20% of the patients had elevated levels, indicating air-trapping. Airway obstruction, as measured by reduced FEV₁ or FEF₂₅₋₇₅ was seen in approximately one fifth of patients (table 1). When more sensitive tests of small airways involvement were performed (FEF₅₀ and FEF₇₅), abnormal values were found in nearly 31% of patients. Displacement of the diaphragm and airway compression by the increased size of the liver and spleen might be the cause for the reduced lung volumes and flows. However, as shown in figure 2, there was no correlation between FRC or RV and liver volume index ($r=0.07$, $p=0.54$; and $r=0.06$, $p=0.62$, respectively). Thus, in some patients increased liver size was associated with

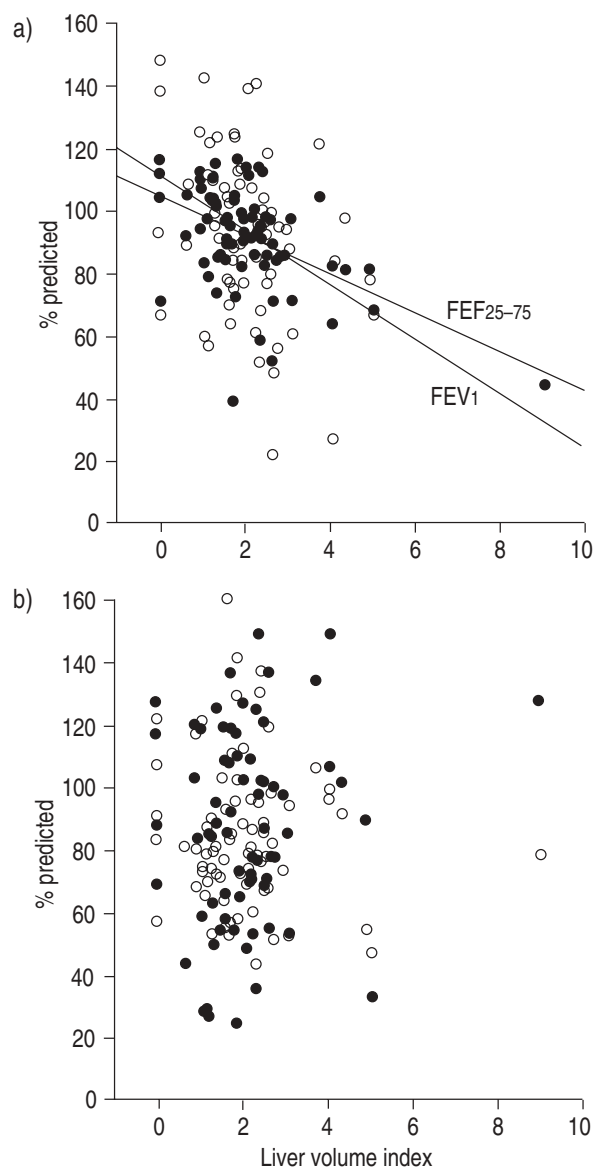


Fig. 2. – Correlation between liver volume index [21] and pulmonary function variables. a) FEV₁ and FEF₂₅₋₇₅ ($r=-0.50$, $p<0.0001$; and $r=-0.38$, $p<0.001$, respectively). ●:FEV₁; ○: FEF₂₅₋₇₅. b) FRC and RV ($r=0.07$, $p=0.54$; and $r=0.06$, $p=0.62$, respectively). ●: FRC; ○: RV. For abbreviations see legend to figure 1.

reduced lung volumes and in others with hyperinflation. Furthermore, there was significant correlation between expiratory flow rates represented by FEV₁ and FEF₂₅₋₇₅ and the liver volume index ($r=-0.50$, $p<0.0001$; and $r=-0.38$, $p<0.001$, respectively). Since no correlation was found between liver volume index and lung volumes, airways abnormalities are likely to reflect the severity of liver involvement rather than its actual size.

In an attempt to assess the association between clinical severity of Gaucher's disease and pulmonary function, 81 of the 95 patients who had complete pulmonary profiles as well as full evaluation of their Gaucher's disease, were divided into two groups: those in whom all values of pulmonary function were normal or minimally reduced as described above ($n=34$; age 31 ± 14 yrs), and those with significantly reduced pulmonary function ($n=47$; age 29 ± 15 yrs). Here too, the proportion of males was similar in each group. Patients with abnormal pulmonary function had a significantly higher severity score indices, SSI and SSNA, than those with normal pulmonary function: SSI in the group with abnormal pulmonary function was 11.7 ± 6.6 versus 7.8 ± 4.9 in the group with normal pulmonary function ($p=0.007$); and SSNA in the group with abnormal pulmonary function was 9.25 ± 5.9 versus 5.6 ± 3.6 in the group with normal pulmonary function ($p=0.007$). Analysis of comparisons between clinical parameters with the presence of specific abnormal pulmonary function is presented in table 2. A high SSI, and even more so a high SSNA, were associated with reduced expiratory flow. It is noteworthy that severity scores of males were not significantly different from those of females: SSI of all males was 11.5 ± 7.1 versus 10.0 ± 5.8 for all females; and SSNA of all males was 8.6 ± 5.6 versus 7.6 ± 5.2 for all females. To isolate the apparent difference between males and females, analysis of variance with sex as a covariate and SSI/SSNA as dependent variables was performed. No sex effect was noted.

Interestingly, male patients had a higher incidence of reduced expiratory flow (as manifested by FEV₁, PEFR, FEF₂₅₋₇₅, FEF₂₅, FEF₅₀ and FEF₇₅) than females (table 3).

Table 2. – P-values for relationship of clinical parameters to the presence of normal or abnormal pulmonary function test (PFT) variables

PFT variable	Sex	Age	Wt	SSI	SSNA
FEV ₁	0.00009	0.47	0.58	0.0001	0.0001
FVC	0.021	0.18	0.67	0.009	0.009
PEFR	0.004	0.014	0.05	0.07	0.02
FEF ₂₅	0.00035	0.034	0.29	0.11	0.13
FEF ₅₀	0.007	0.51	0.93	0.006	0.0009
FEF ₇₅	0.0004	0.96	0.9	0.004	0.0002
FEF ₂₅₋₇₅	0.0099	0.96	0.42	0.072	0.04
FRC	0.44	0.74	0.63	0.17	0.1
RV	0.82	0.99	0.21	0.06	0.12
TLC	0.51	0.19	0.65	0.03	0.08
RV/TLC	0.64	0.03	0.91	0.37	0.26
Kco	0.76	0.03	0.59	0.008	0.0013

Tests which were used were chi-squared for sex, Student t-test for age and weight (Wt), and Mann-Whitney for SSI and SSNA. For abbreviations see legend to table 1.

Table 3. – Proportions of abnormal pulmonary function variables among males and females

	Males %	Females %	p-value
n	36	59	
FVC	29	10	0.02
FEV ₁	36	5	0.0001
PEFR	22	3	0.004
FEF ₂₅₋₇₅	36	11	0.002
FEF ₂₅	36	7	0.0003
FEF ₅₀	47	21	0.007
FEF ₇₅	47	14	0.0004
TLC	25	19	0.51
RV	19	18	0.81
RV/TLC	14	18	0.64
FRC	56	47	0.44
Kco	44	40	0.76
All variables	73	48	0.02

For abbreviations see legend to table 1.

Of the 24 children between the ages of 7 and 16 years (25%), no increased incidence of abnormal pulmonary function was noted relative to adults. In this group of children, the ratio of males (42%) was similar to the adult cohort (38%). Of the 77 patients in whom smoking status was available, only seven had a history of smoking. All had normal FEV₁ and normal lung volumes, Kco was reduced in two of them.

Eighty one patients had chest radiographs: 67 (83%) had normal chest radiographs; nine patients (11%) had grade 1 involvement; and three patients (4%) had grade 2 involvement. Six of the patients with grade 1 involvement and one patient with grade 2 had reduced Kco. Two patients (3%) had radiographic signs of pulmonary hypertension, which were subsequently confirmed by Echo-Doppler cardiography (estimated pulmonary artery pressure of 52 and 43 mmHg). Both had severely abnormal pulmonary function.

There was no correlation between specific genotype and increased incidence of abnormal pulmonary function. However, most of our patients had the 1226G/1226G genotype, with high intragenotype variability which hampered proper comparison with other genotypes.

Discussion

Our study demonstrates a high incidence of abnormal pulmonary function in type I Gaucher's disease. Abnormal pulmonary function, which has previously been regarded as an atypical, albeit serious, complication, should now be re-evaluated as more pernicious to the heterogeneous pattern of Gaucher symptoms. The direct correlation between the severity score index and the degree of lung involvement and the correlation between liver size and airways obstruction indicate that pulmonary disease is part of the general severity of the disease and not an isolated finding.

Reduction in diffusion capacity was found in 42% of the patients. It was not associated with clinical symptoms

in most of the cases. K_{CO} reduction in Gaucher's disease is likely to result from accumulation of Gaucher cells in the alveolar spaces, and their infiltration into the alveolar walls and the perivascular septal regions, causing, in some of the cases, interstitial fibrosis [8]. Reduced pulmonary vascular bed secondary to capillary plugging or pulmonary hypertension can also cause low diffusion capacity. Apparent pulmonary hypertension was found in 3% of our patients. Since echocardiography was not performed routinely in all the patients, we do not know whether pulmonary hypertension contributed to the low diffusion capacity in some patients. This serious complication is progressive in nature, and may be fatal. Gaucher cells were reported to obstruct pulmonary capillaries and cause pulmonary hypertension [8]. Pulmonary hypertension in Gaucher's disease can also result from chronic hypoxaemia secondary to interstitial disease, to liver disease, to long bone infarction and fracture with pulmonary emboli.

In the more severe cases, reduction of lung volumes occurs, which was found in approximately 20% of the patients. The reduced FRC found in half of the patients is likely to be secondary to the enlarged liver and/or spleen, with upward displacement of the diaphragm. Small airways functional abnormalities were found in approximately one fifth of the patients. In contrast to lung volume parameters, reduced expiratory flow rates correlated with liver size and with the severity score index, thus, indicating that other causes beside mechanical compression of the lung cause the pulmonary function abnormalities. Airways obstruction in Gaucher disease can be caused by peribronchial and terminal bronchiolar infiltration, or bronchial and bronchiolar compression by infiltration of adjacent pulmonary parenchyma, or by enlarged lymph nodes [8]. Thus, the small airways functional abnormalities observed in our study are likely to be part of the general severity and organ involvement, and not secondary to diaphragmatic displacement by the enlarged intra-abdominal organs. We cannot explain why small airway obstruction parameters were more often reduced in males than in females.

Many patients with abnormal pulmonary function had no respiratory symptoms; this raises questions about the clinical significance of these abnormalities. Progressive cardiorespiratory exercise studies may be used to further investigate the relevance of these pulmonary function abnormalities. Meanwhile, patients with significant pulmonary abnormalities should be advised of the manifestations of hypoxaemia due to exercise, high altitudes, and during flights. In addition, Gaucher patients with abnormal pulmonary function need to be followed in order to identify progression of their lung disease.

Type I Gaucher patients with pulmonary involvement appear to have more severe manifestations in other organs. It has previously been shown that severe organ involvement was associated with certain genotypes. We did not find correlation between abnormal pulmonary function and specific Gaucher genotype. However, since 90% of all patients studied had the common "mild" genotype (1226G/1226G), it was impossible to extrapolate the genotype-phenotype relationship with regard to lung

involvement. It should be noted that all affected children under 6 yrs of age were eliminated in this study, most of whom suffered from severe Gaucher's disease and had other genotypes. Likewise, the two symptomatic patients with severe pulmonary disease and pulmonary hypertension were compound heterozygotes. Therefore, the lack of correlation between pulmonary function and genotype in this study may not reflect the reality in Gaucher's disease.

Recently, BEUTLER *et al.* [23] and PELINI *et al.* [24] reported that pulmonary disease was improved, as documented by amelioration in oxygenation and diffusion capacity, in patients with type I Gaucher's disease with severe pulmonary involvement (two of whom had been on continuous nasal oxygen therapy because of severe dyspnoea), upon initiation of enzyme replacement therapy. The therapeutic value of enzyme replacement therapy in reducing signs and clinical symptoms of lung disease in type I Gaucher's disease seems to be promising, however, it needs to be investigated further in a larger number of patients.

In conclusion, pulmonary function abnormality is common among type I Gaucher patients. These abnormalities include alveolar-capillary diffusion abnormality, small airways obstruction with reduced expiratory flows, and reduction in lung volumes. These findings imply that there is incipient lung involvement in type I Gaucher's disease, despite the lack of clinical signs and symptoms. The nature of these previously unrecognized abnormalities is still poorly understood, especially as it affects several possible pathophysiological mechanisms. Its rate of progression and clinical significance need to be determined. In view of the large proportion of patients with abnormal pulmonary function observed in our study, we recommend that pulmonary function tests should be performed as part of the routine evaluation of Gaucher patients, and before enzyme replacement therapy is initiated.

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