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Different features of lung involvement in Niemann-Pick disease and Gaucher disease

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Summary
Background: Niemann-Pick disease (NPD) and Gaucher disease (GD) are well-known lysosomal storage diseases. Respiratory system involvement is an important cause of morbidity and mortality in patients with NPD and GD.
Objectives: We tried to assess the clinical, radiological, and histological features of GD and NPD patients with lung involvement.
Methods: We reviewed medical history, physical examination, radiological, and histological data of 10 NPD and 7 GD patients.
Results: The most common respiratory symptoms were recurrent lung infection and dyspnea. Although lung examination results in 6 NPD patients were normal, they had lung involvement; 3 patients were diagnosed as NPD directly via lung biopsy during investigation of recurrent lung infection or interstitial lung disease. All GD patients but 1 had respiratory system symptoms at the time of diagnosis. Hepatopulmonary syndrome was present in 4 GD patients. A ground-glass pattern and atelectasis were 2 important high-resolution computed tomography features in the NPD and GD patients. Flexible bronchoscopy and bronchoalveolar lavage were used for emergency extraction of bronchial casts in 1 NPD patient.
Conclusions: Lung involvement in NPD and GD patients should be included in the differential diagnosis of interstitial lung disease. Besides interstitial appearance on HRCT, atelectasis related to bronchial cast and bronchiectasis are other radiological findings in these

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group of patients. Analysis of bronchoalveolar fluid and lung biopsy provide very important clues for diagnosis. Hepatopulmonary syndrome is an important vascular complication observed in GD patients.

Introduction

Lysosomes are intracellular organelles that contain a variety of hydrolytic enzymes and degrade complex macromolecules, including glycosaminoglycans, sphingolipids, glycoproteins, and glycogen. Lysosomal storage diseases are caused by deficiency of one or more of these enzymes. As a result of such deficiency, the substrate (or substrates) normally degraded by lysosomes accumulate in various organs, including the liver, spleen, lungs, and brain.[1]

Niemann-Pick disease (NPD) is an important lysosomal storage disorder which is inherited in an autosomal recessive manner and has a frequency of approximately 1 in 100,000 births. Symptoms of NPD are due to the accumulation of lipid-laden macrophages (Niemann-Pick cells) in such organs as the liver, spleen, bone marrow, brain, and lungs. NPD has 3 primary variants, based on metabolism and clinical symptoms. Type A and type B result from inherited deficiency of sphingomyelinase. Type C is due to defective cholesterol transport. Lung involvement may be a feature of NPD; however, the precise incidence is unknown because the literature consists mostly of small patient series.[1]

Gaucher disease (GD) is a multisystemic lipidosis, characterized by organomegaly, hematologic problems, and skeletal involvement. It is an autosomal recessive disease resulting from deficient activity of a lysosomal enzyme (glucocerebrosidase). Because of the deficient enzyme activity glucocerebroside accumulates in macrophages and the reticuloendothelial system. According to the presence or absence of neurologic manifestations, 3 clinical subtypes have been described (types 2-3 and 1, respectively).[2] Lung involvement is not common at presentation and is correlated with severe forms of the disease. Respiratory problems result from infiltration of alveolar, interstitial, perivascular, and peribronchial spaces by lipid-laden macrophages (Gaucher cells).[3] As a complication of chronic liver disease arteriovenous shunting (hepatopulmonary syndrome) may also be observed.[4] Patients that are homozygous for 1448G (L444P) mutation may have an additional risk for lung involvement.[5]

In order to assess the clinical, radiological, and histological features of GD and NPD patients with lung involvement, we reviewed medical history, physical examination, radiological, and histological data of 17 patients (10 NPD, 7 GD) that were followed-up at a tertiary referral clinic in Turkey.

Materials and methods

Patients

The medical files of NPD and GD patients diagnosed between 1981 and 2010 at Hacettepe University, İhsan Doğramacı Children's Hospital were reviewed retrospectively. In total, 73 GD and 40 NPD patients were followed between 1981 and 2010 and a total amount of 23 NPD and GD patients had lung involvement (20.3%). The study included 10 NPD and 7 GD patients with lung involvement who have complete data, as determined based on clinical features, radiological findings, or bronchoalveolar lavage (BAL) fluid analysis, that were followed-up by the pediatric gastroenterology and pulmonology departments. Three patients were biopsied during the process of investigation for diffuse parenchymal lung disease and were diagnosed as NPD-related lipoid pneumonia. Further enzymatic analysis showed acid sphingomyelinase (ASM) deficiency. On the other hand, 7 of the NPD patients were previously diagnosed as NPD and during follow-up developed symptoms and signs of accumulation of Niemann-Pick cells in the lungs. Further radiological investigation and BAL fluid analysis results proved respiratory system involvement. Diagnosis of NPD type A and type B was confirmed in each patient via documentation of reduced ASM activity in isolated leukocytes and/or cultured skin fibroblasts. The presence or absence of early neurological degeneration led to differentiation of type A or type B NPD. The diagnosis of type C NPD was based on abnormal intracellular esterification of cholesterol, which is derived from exogenous lipoprotein-derived cholesterol, measured in cultured fibroblasts obtained via skin biopsy. Bone marrow aspiration was performed in all patients and Wright stain was used for the identification of sea-blue histiocytes before enzymatic analysis. Bone marrow aspiration was performed in all patients for identification of Gaucher cells. The diagnosis of GD was confirmed via documentation of a deficient acid β-glucosidase level in leukocytes and by mutation analysis. The presence or absence of neurological findings in the patients' histories and physical examination results facilitated determination of the subtypes of GD. Seven patients were diagnosed with GD; 4 had type 1 and 3 had type 3.

Respiratory investigations

Chest X-rays (CXRs), thoracic high-resolution computed tomography (HRCT), and respiratory function tests were performed, according to the standard techniques used at our hospital. All patients had at least 1 CXR during their follow-up. HRCT was performed in 8 NPD patients and 4 GD patients (Table 1).

Flexible bronchoscopy and BAL were performed in 4 NPD patients (2 type C, 1 type A, and 1 type B) by skilled pediatric pulmonologists. A standard method was used to collect BAL fluid. In the diagnostic work-up for interstitial lung disease, surgical lung biopsy was performed in three patients. Hematoxylin-eosin stain and May-Grünwald Giemsa stain were used for identification of storage cells.

Table 1 Clinical characteristics of the Niemann-Pick disease patients with lung involvement.

Patients no.-gender	Type	Con	Age at diagnosis	Respiratory findings at diagnosis	Organs involved	HRCT	Duration of follow-up	Mutation	Last follow-up
1-F	A	+	4.5 mo	Recurrent lung infection PE: Normal	Lung, liver, spleen, CNS	ND	2.5 yr	GS P189/ GS P189	Deceased
2-F	B	−	16 mo	Isolated dyspnea, recurrent lung infection, PE: fine crackles, cyanosis	Lung, liver, spleen	GGO	1 yr	ND	Stable
3-M	B	+	11 mo	Chronic cough PE: Diminished lung sounds prominent on lower lobes	Lung, liver, spleen	Bilateral interstitial infiltration	3 yr	ND	Stable
4-F	B	−	18 mo	Respiratory failure PE: Cyanotic, clubbing, fine crackles:	Lung, liver, spleen	Widening of pulmonary arteries/veins in lower right lung	19.5 yr	GS P189/ L187 P	Deceased
5-M	B	+	3 mo	None PE: Normal	Lung, liver, spleen	GGO	11 yr	L 137P / L 137P	Stable
6-F	B	+	8 yr	None PE: Normal	Lung, spleen	ND	1 yr	ND	Oxygen support
7-F	B	+	9 yr	None PE: Normal	Lung, liver, spleen	Atelectasis in lingula, bronchiectasis in lingula and lower lobe of left lung	2 yr	ND	Stable
8-M	B	+	9 yr	Dyspnea, productive cough PE: Tachypnea	Lung, liver, spleen	GGO	2 yr	ND	Stable
9-F	C	+	6 yr	None PE: Normal	Lung, spleen	Bilateral reticulonodular appearance	1 yr	ND	Stable
10-M	C	+	11 mo	Recurrent lung infection PE: Normal	Lung, liver, spleen	Atelectasis in upper right lung	9 mo	ND	Stable

F: Female; M, Male; Con, Consanguinity; mo, months; yr, year(s); PE, Physical examination of respiratory system; sPO_2, Transcutaneous oxygen saturation while breathing room air; GGO, Ground-glass opacification; CNS, Central nervous system; ND, Not done.

To diagnose hepatopulmonary syndrome contrast echocardiography was performed in the pediatric cardiology unit.

Results

Clinical and radiological data

Niemann-Pick disease

Fourteen patients had lung involvement. In total, 4 patients were excluded from the study due to incomplete data; 10 NPD patients (4 boys, 6 girls; patients 1—10) with lung involvement were included in the study. Patients' clinical data are summarized in Table 1. Among them, 1 patient was classified as type A, 7 as type B, and 2 as type C. Age at diagnosis of NPD ranged between 3 months and 9 years (median: 17 months). Parental consanguinity was present in all of the NPD patients, except patient 2 and 4. Six patients had respiratory complaints at the time NPD was diagnosed. Respiratory symptoms at diagnosis included isolated dyspnea, chronic cough, recurrent lung infections, and respiratory failure. The most common respiratory symptoms were recurrent lung infection (3 patients) and dyspnea (2 patients). Patients 1, 2, and 10 suffered from recurrent lung infections that were responsive to antibiotics. On the other hand, patients 5, 6, 7, and 9 did not have any signs of respiratory system involvement at the time of diagnosis, and did not develop any symptoms during follow-up; however; radiological evidence was obtained during investigation of different clinical problems. Respiratory system examination results in 6 of the NPD patients were normal, whereas 4 patients had positive findings (Table 1). One of the symptomatic patients died due to respiratory failure at the age of 21 years after 19.5 years of follow-up; she was diagnosed as NPD type B at the age of 1.5 years and her respiratory problems (cyanosis, clubbing, fine crackles) began at the age of 12 years. In the present series there was only one NPD type A patient. She was diagnosed at the age of 4.5 months following the onset of recurrent lung infections. BAL was performed to determine the etiology. Macroscopic examination showed opalescent fluid originating from all bronchial openings. The most characteristic finding in the BAL fluid analysis was foamy histiocytes. Median follow-up period of all NPD patients was 2 years.

Chest X-rays in all but 1 NPD patient (patient 7) exhibited an interstitial appearance on bilateral lung fields. CXR in patient 8 showed segmental atelectasis on the left lung. HRCT was performed in 8 of the 10 NPD patients (Fig. 1) and showed predominant ground glass opacification (GGO) in 3 patients. Interestingly, in 2 patients (patients 8 and 10) HRCT showed atelectasis (Table 1). Patient 4's CXR exhibited a bilateral reticulonodular appearance and elevated left hemidiaphragm, and fluoroscopy showed left hemidiaphragm paralysis. Thoracic high-resolution computed tomography was performed in this patient in order to investigate any possible lung involvement. It showed thickening of the interlobular septae and axial interstitium. Additionally, there was widening of the pulmonary veins, especially in the lower lobes of both lungs. Echocardiography and catheter angiography confirmed multiple pulmonary arteriovenous fistulas on the lower lobes of both lungs and pulmonary hypertension. Pulmonary artery pressure was 33/12 mmHg (mean: 24 mmHg). Pulmonary function test results of NPD patients were noted in Table 3. At the time of research, seven patients were stable whereas one patient was on continuous oxygen support. Two out of ten NPD patients died due to cardiac and respiratory failure (Table 1).

Gaucher disease

Patients' clinical data are summarized in Table 2. Nine children with GD had lung involvement and 2 were excluded from the study because of incomplete data. In total, 7 GD patients (4 girls, 3 boys; patients 11—17) with lung involvement were included in the study. Among them, 4 were born to non-related parents and none received enzyme replacement therapy. All patients except patient no.15 had respiratory symptoms at the time of diagnosis. Patient 15 did not develop any respiratory symptoms during his follow-up; however, his CXR and HRCT findings indicated lung involvement (Table 2). Hepatopulmonary syndrome (HPS) was noted in 4 (patient no. 11, 13, 14, 15) of the 7 GD patients based on contrast echocardiography. Median follow-up period of all GD patients was 9 years.

Chest X-rays in all the GD patients showed diffuse interstitial infiltration in both lung fields. HRCT in 2 GD patients showed a predominant ground-glass pattern and superimposed thickening of interlobular septa. Patient 16's HRCT showed only focal atelectasis on the lower lobe of the right lung, whereas patient 13 had normal HRCT findings (Table 2). Pulmonary function test results of GD patients were noted in Table 3.

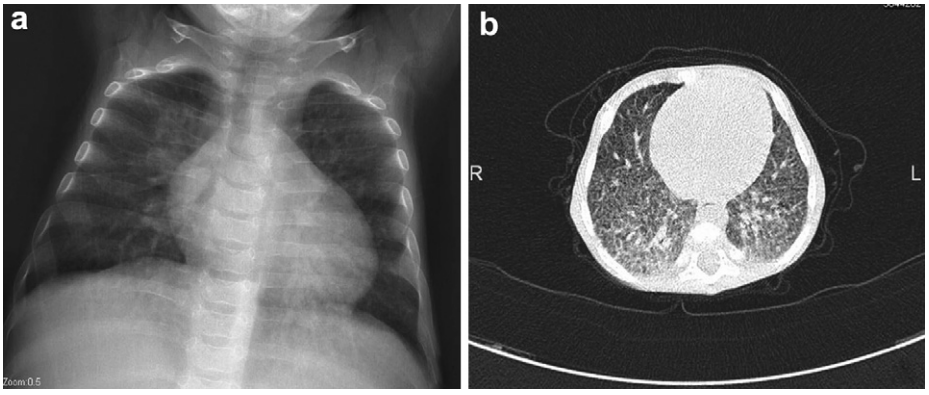

Figure 1 CXR (a) and HRCT (b) of patient no. 3.

Table 2 Clinical characteristics of the Gaucher disease patients with lung involvement.

Patients no.-gender	Type	Con	Age at diagnosis	Respiratory findings at diagnosis	Organs involved	HRCT	Duration of follow-up	Mutation	Last follow up
11-F	1	−	4 yr	None PE: Cyanosis	Liver, spleen, skeleton, lung	ND	9 yr	N370S/L444P	Oxygen support
12-F	1	−	2.5 yr	Chronic cough, recurrent lung infection PE: Clubbing, cyanosis	Liver, spleen, skeleton, lung	ND	14 yr	N370S/-	Oxygen support
13-M	1	+	5 yr	Dyspnea, productive cough PE: Clubbing	Liver, spleen, lung, skeleton	Normal	8 yr	N370S/-	Oxygen support
14-F	1	+	2.5 yr	Cyanosis PE: clubbing	Liver, spleen, lung	ND	10 yr	N370S/-	Deceased
15-M	3	+	10 mo	None PE: Normal	Liver, spleen, lung	GGO, interlobular septal thickening	9 yr	L444P/L444P	Deceased
16-M	3	−	11 mo	Recurrent lung infection PE: Normal	Liver, spleen, lung, skeleton	Atelectasis on lower lobe of right lung	4 yr	L444P/L444P	Deceased
17-F	3	−	12 mo	Dyspnea, peripheral cyanosis, productive cough PE: Clubbing	Liver, spleen, lung, skeleton	GGO, interlobular septal thickening	7 yr	L444P/L444P	Deceased

F: Female; M, Male; Con, Consanguinity; mo, months; yr, year(s); PE, Physical examination of respiratory system; sPO_2, Transcutaneous oxygen saturation while breathing room air; GGO, Ground-glass opacification; ND, Not Done.

Table 3 Available pulmonary function test results of patients with Niemann-Pick disease and Gaucher disease.

Patient No.	Type	FVC (%pred)	FEV_1 (% pred)	FEV_1/FVC (% pred)
3	NPD Type B	83	91	100
4	NPD Type B	40	39	102
6	NPD Type B	76	73	83
8	NPD Type B	104	86	78
13	GD type 1	78	83	107
15	GD type 1	45	45	95

Overall prognosis of GD patients were worse than NPD patients, three patients were on continuous oxygen support. Unfortunately, four patients died due to cardiac and respiratory failure (Table 2). None of the patients received enzyme replacement therapy.

Bronchoalveolar lavage analysis

Flexible bronchoscopy and BAL were performed in 4 NPD patients (patients 1, 8, 9, and 10) and 2 GD patients (patients 16 and 17). Lipid-laden macrophages were shown in all patients who underwent bronchoscopy. Flexible bronchoscopy was performed in patient 8 initially to diagnose lung involvement. When he developed acute severe respiratory failure, CXR showed total atelectasis (Fig. 2) and he underwent emergency bronchoscopy. Bronchial cast formation was observed in the right bronchus (Fig. 3) and after removal of the casts via gentle aspiration and whole-lung lavage the patient's symptoms resolved. Follow-up CXRs (Fig. 2) showed resolution of atelectasis.

Histological analysis

In all, 3 patients were diagnosed as NPD directly via lung biopsy during investigation of recurrent lung infection or interstitial lung disease. Patients 2 and 8 suffered from recurrent "lung infections" that began at 4 and 12 months of age, respectively. They were both hospitalized several times and routine etiologic investigation did not reveal any possible cause. Patient no. 2 did not accept flexible bronchoscopy and lung biopsy was performed. On flexible bronchoscopy of patient no. 8, bronchial casts were extracted from both lungs. And lung biopsy was performed for etiological purposes. Microscopic examination showed foamy histiocytes in the alveolar spaces and interstitial tissue (Fig. 4). Interstitial fibrosis was not observed; there were only scattered lymphocytes.

Patient 6 was an eight-year-old girl was admitted to our center for evaluation of a diffuse reticulo-nodular appearance of both lungs on CXR. She had been underweight since infancy. Her spleen was palpabl 8 cm below the costal margin. The liver was not palpated. The neurological examination was normal. Routine investigation did not reveal any etiological cause. Because of the fact that flexible bronchoscopy was not available at that time, an open lung biopsy was performed due to the

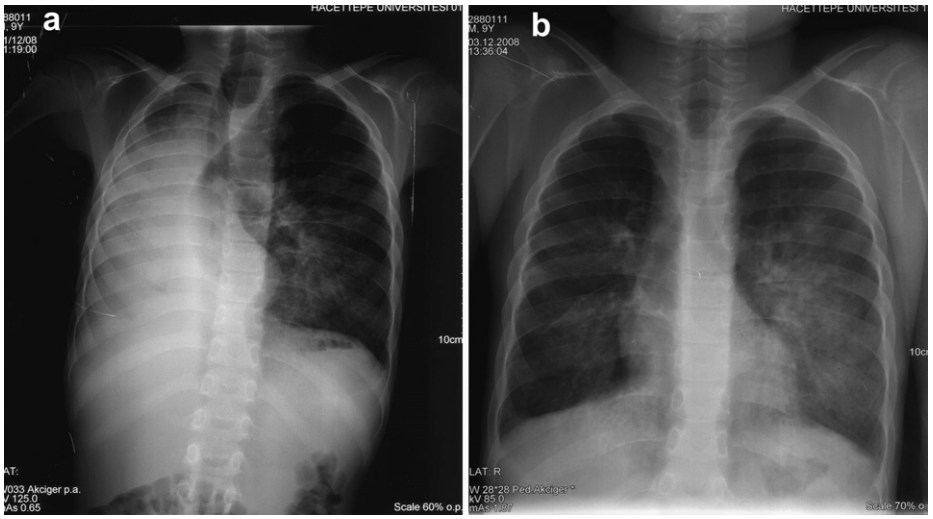

Figure 2 CXR of patient 8 before (a) and after (b) Bronchoscopy.

suspicion of miliary tuberculosis. Microscopic examination showed nodular clusters of oil-red O- and Sudan-black B-positive foamy histiocytes in the alveoli, located primarily in the perivascular, peribronchial, and subpleural regions. A Wright-stained bone marrow specimen showed many foamy histiocytes.

Discussion

The present study aimed to assess the clinical, radiological, and histological features of NPD and GD patients diagnosed at a referral center in Turkey. Lung involvement was reported in all types of NPD, including type A. A recent study that included 10 infants with type A NPD reported the onset of respiratory system involvement at a median age of 9 months.[6] Similarly, another case series of 13 patients reported that only 1 patient was diagnosed as type A NPD.[1] In our series, there was only one NPD type A patient. She died at the age of 3 years due to severe respiratory insufficiency.

In contrast to type A, type B NPD has a more variable course. Lung involvement is typically asymptomatic and is observed primarily in adult patients following evaluation of mild respiratory system complaints.[7–10] Respiratory system involvement in such patients is variable; some patients exhibit mild respiratory symptoms such as recurrent cough[11]; however, severe and fatal lung disease is also reported. In series of McGovern et al., shortness of breath and pulmonary infections are two frequent symptoms (42% each). And 20% of the patients had respiratory disease at presentation.[12] Lung involvement is also detected during evaluation of respiratory symptoms, such as dyspnea, chronic cough, and recurrent lung infections. In the present study 7 type B NPD patients had lung involvement; 3 patients were completely asymptomatic with normal lung examination results; however, during follow-up they developed radiological or histological signs of lung involvement. Respiratory function tests of our patients were normal or restrictive.

Guillemot et al. reported 13 NPD patients with lung involvement and two of them were type C NPD.[1] They both had severe neurological involvement and developed

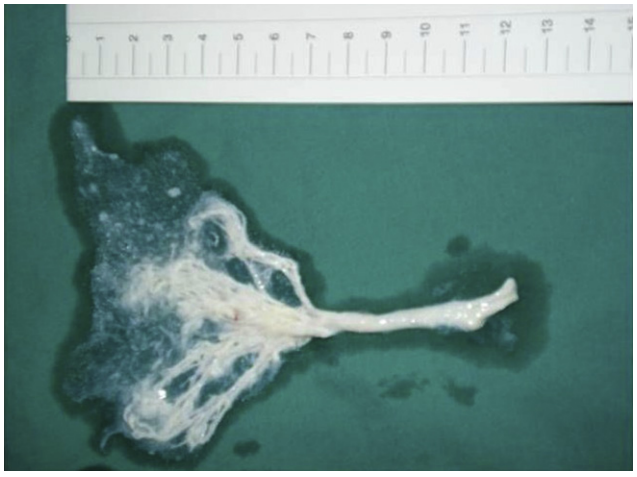

Figure 3 Extracted bronchial cast of patient 8.

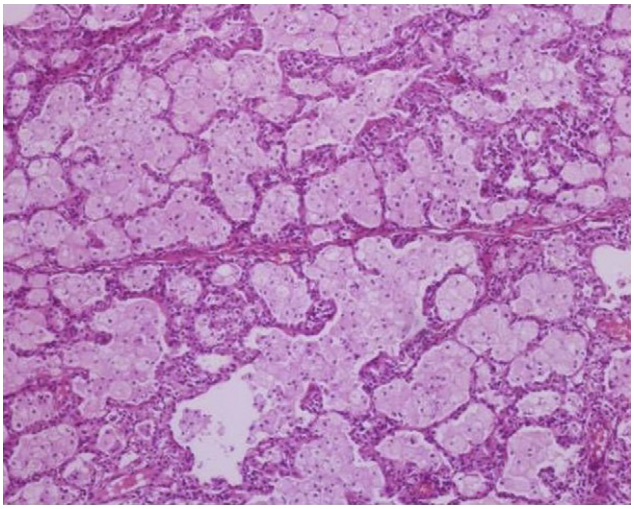

Figure 4 Foamy histiocytes in the alveoli and interstitial tissue (hematoxylin-eosin, original magnification 100×).

pulmonary symptoms within the first months of life that progressed to severe respiratory failure before the age of 3 years. One of these patients died at the age of 3 years and the other was lost to follow-up. In the present study there were 2 type C NPD patients; one did not have any respiratory system complaints or findings at the time of diagnosis, only radiological evidence, whereas the other presented with recurrent lung infections. At the last follow-up they were both stable, although their follow-up was relatively short (9 months and 1 year). Although recurrent lung infections are described for all of the NPD types, alterations of the immune responses are more abundant in type C disease.[13]

Two treatment modalities have been described for lung involvement in NPD patients. Bone marrow transplantation was reported to be successful in decreasing pulmonary infiltrates.[14] Whole lung lavage was also reported to be an effective treatment, especially in adults[15,16]; however, results in children differ. Uyan et al. reported a 3-month-old girl diagnosed as type B NPD with lung involvement.[17] Unilateral lung lavage was performed; however, she did not improve clinically or radiologically, and died at the age of 15 months. There are no data about enzyme replacement therapy or substrate reduction therapy for patients with lung involvement of NPD and none of our patients received any of them.

In the present study BAL was performed in NPD patients for diagnostic (patients 1, 8, 9, and 10) and therapeutic purposes (patient 8). An advantage of BAL is the avoidance of performing lung biopsy for determining lung involvement. Three out of ten NPD patients underwent lung biopsy. All biopsy procedures were performed for the differential diagnosis of recurrent lung infection or due to a reticulonodular pattern on CXR.

Chest X-ray and CT scans are not specific for the diagnosis of lung involvement in NPD and GD patients. Mendelson et al. investigated the CXR and thin-section CT features of 53 NPD patients with lung involvement.[18] Evidence of interstitial lung disease (interstitial thickening and ground-glass appearance) was commonly observed with thin-section CT scans. In the present study the most common CT abnormality was ground-glass appearance. Patients 7 and 10 had atelectasis on HRCT. More interestingly, patient 7 also had bronchiectasis in the lingula and left lower lobe. Bronchoscopy showed a white mucous plug that was prominent in the left upper lobe and lingula. To the best of our knowledge this is the first report of an NPD patient with bronchiectasis. A study performed with ASM-deficient mice reported continuous pulmonary inflammation and increased cellular infiltrates, which resulted in alteration in surfactant composition. Abnormal surfactant and inflammation contribute to lung abnormalities,[19,20] which we think may have been the cause of bronchiectasis in our patient.

In the present study there were 7 GD patients; 3 with neurological involvement and 1 (patient 15) without any respiratory system complaints and normal physical examination results, whose HRCT showed GGO and interlobular septal thickening.

Santamaria et al. suggested that patients with GD that are homozygous for the L444P mutation might have an increased risk for lung involvement.[5] In the present study 3 patients with type 3 GD were homozygous for L444P. On the other hand, 3 GD patients were heterozygous for N370S, which is a predictive mutation for type 1 disease, and 1 patient was compound heterozygous for N370S/L444P. Emre et al.[21] reported that the most prevalent glucocerebrosidase mutations in Turkish patients were L444P and N370S, which is consistent with the present study's findings. More than 50% of GD patients die due to respiratory failure, and the remainder require continuous oxygen support. In addition, all of the present study's patients that were homozygous for L444P died due to respiratory failure.

As a serious complication of long-standing liver disease in GD patients, arteriovenous shunting can also be observed.[4,22] Hepatopulmonary syndrome is associated with severe hypoxemia in the setting of hepatic dysfunction and intrapulmonary vascular dilatation. This dilatation is the one of the major features of hepatopulmonary syndrome and is the main cause of hypoxemia in such patients. This dilatation is thought to be a result of failure of the liver to clear circulating pulmonary vasodilators and inhibition of circulating vasoconstrictive substances.[4] In the present study contrast echocardiography showed that 4 of the 7 GD patients had hepatopulmonary syndrome. It is an important vascular complication of GD and may contribute to the worse prognosis of lung involvement in GD patients in our series. None of our patients received enzyme replacement therapy or substrate reduction therapy. Goitein et al. reported their experience of enzyme therapy in lung involvement of GD and pointed out the heterogeneity in response to this type of treatment.[2] Schiffmann et al. reported an improvement in pulmonary function test results in GD type 3 patients receiving substrate reduction therapy (miglustat) in addition to enzyme replacement therapy.[23]

The present study's limitation is its retrospective design; however, the findings show that both NPD and GD can cause important respiratory system signs and symptoms, both at diagnosis and during follow-up. Lung involvement in patients with NPD and GD should be included in the differential diagnosis of interstitial lung disease; lung biopsy provides very important diagnostic clues. Microscopic analysis of BAL fluid is another diagnostic tool and may show foamy macrophages, which are not pathognomonic but suggestive of NPD and Gaucher cells, indicating GD. Bronchial casts can be observed as a feature of NPD and may cause significant respiratory distress and extraction of bronchial casts and whole-lung lavage facilitate clinical and radiological improvement in such patients. Overall prognosis was worse in the GD patients; however, this might have been due to the NPD patients' shorter follow-up period.

Conflict of interest

The authors of the manuscript did not declare any competing interest.

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