C A S E R E P O R T

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Pulmonary involvement in siblings with Gaucher disease type III

Plućne manifestacije kod srodnika sa Gošeovom bolesti tip III

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Abstract

Introduction. Pulmonary involvement has been described in all types of Gaucher disease (GD) but it is considered as relatively rare manifestation. There are reports suggesting that homozygosity for L444P mutation in GBA gene is associated with a substantial risk for developing primary pulmonary disease in GD. **Case report.** We reported sisters with pulmonary involvement in GD type III. Respiratory failure with fatal outcome at 3 years and 4 months of age occurred in K.K. due to pulmonary complications of GD. At the time enzyme replacement therapy (ERT) was not available in Serbia. J.K., homozygous for L444P mutation, developed asymptomatic pulmonary involvement at the age of 6 after 2.5 years of ERT. Pulmonary disease in J.K. was verified by high resolution computerized tomography, cytology of bronchoalveolar lavage fluid and histopathology of transbronchial lung biopsy. **Conclusion.** Primary lung disease in children homoallelic for L444P mutation in GBA gene emerges as a significant clinical manifestation of GD with unclear response to ERT.

Key words:
gaucher disease; genetic diseases, inborn; mutation; lung diseases; treatment outcome.

Apstrakt

Uvod. Plućne manifestacije opisane su kod sva tri tipa Gošeove bolesti, ali se smatraju relativno retkom komplikacijom ove nasledne bolesti. Pojedine studije ukazuju da homozigotnost za mutaciju L444P u genu GBA predstavlja faktor rizika od razvijanja primarnog plućnog zahvatanja u sklopu Gošeove bolesti. **Prikaz slučaja.** Prikazali smo sestre sa plućnim komplikacijama Gošeove bolesti. Respiratorna insuficijencija i smrtni ishod u uzrastu od tri godine i četiri meseca kod devojčice K.K. objašnjeni su plućnim komplikacijama Gošeove bolesti. U to vreme enzimska supstituciona terapija nije bila dostupna u Srbiji. Njena sestra J.K, L444P homozigot, razvila je asimptomatske plućne manifestacije u uzrastu od šest godina, nakon dve i po godine enzimske supstitucione terapije. Plućna bolest potvrđena je visokorezolutivnom kompjuterizovanom tomografijom (KT) pluća, citološkim pregledom bronhoalveolarnog lavata i histopatološkim pregledom uzorka dobijenog transbronhijalnom biopsijom pluća. **Zaključak.** Primarna plućna bolest kod dece homozigotne za L444P mutaciju u genu GBA ističe se kao značajna klinička manifestacija Gošeove bolesti sa nedovoljno jasnim odgovorom na enzimsku terapiju.

Ključne reči:
gošeova bolest; nasledne bolesti; mutacija; pluća, bolesti; lečenje, ishod.

Introduction

Gaucher disease (GD) is an autosomal recessive lysosomal storage disorder caused by deficient activity of beta-glucocerebrosidase [1]. Mutations in the glucocerebrosidase gene (GBA) lead to a decreased enzymatic activity and accumulation of glucocerebroside within cells of mononuclear phagocyte origin which present as typical Gaucher cells in affected tissues. Pulmonary involvement has been described in all three types of disease, but considered as relatively rare manifestation of GD [2]. Clinically significant lung disease in most cases correlates with overall severity of the disease and is mainly seen in children with neuronopathic forms of GD (types II and III) [3]. However, pulmonary function testing revealed abnormalities in up to 68% of GD type I patients regardless of having clinical signs of pulmonary involvement [4]. There are reports suggesting that homozygosity for the mutation L444P (encoding the substitution of proline for leucine

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at position 444 of the enzyme) is associated with a substantial risk of developing primary pulmonary disease in GD [5]. Beneficial effects of enzyme replacement therapy (ERT) on pulmonary involvement in GD seem to be absent or moderate in the majority of cases [3, 6, 7].

Case report

We reported two sisters diagnosed with GD type III who were born to non-consanguineous parents from the western Serbia. K.K. was the first-born child in this family and presented to our Institution at the age of 12 months with enlargement of the liver and spleen. The diagnosis of GD was established after a bone marrow examination revealed the presence of Gaucher cells. At the time ERT was not available in Serbia. Regarding the presence of oculomotor apraxia, type III of GD was suspected. During the following two years the girl developed massive hepatosplenomegaly and repeatedly suffered of lower respiratory tract infections with radiographic findings of chronic interstitial lung disease. At 3 years and 4 months of age the chied was admitted at our Institute for progressive dyspnoea. Chest radiography examination revealed bilateral reticulonodular pattern of infiltration in lungs. She succumbed to respiratory failure several days later. *Post-mortem* examination was disallowed by family due to religious reasons. Retrospectively, severity score index (SSI) for GD was estimated to 21.

The other sister J.K. was born two years after the fatal outcome in K.K. Previously, the parents declined referral to genetic counseling. She was diagnosed with GD at two years of age on the basis of bone marrow infiltration with Gaucher cells and low leukocyte ß-glucosidase activity. Genetic testing (mutation analysis in Biochemical laboratory of University of Amsterdam) revealed that J.K. was homozygous for L444P mutation. Initial manifestations of disease included massive hepatomegaly and splenomegaly, hematologic abnormalities (thrombocytopenia, anemia), growth retardation and oculomotor apraxia as only neurological sign. That patient was assigned with moderate SSI of 16 at the onset of disease. There were no clinical nor radiological signs of intrinsic pulmonary disease within GD at the time. Enzyme replacement therapy was started with imiglucerase at the age of four years with dose of 120 IU/kg/month. After two years of ERT dose was increased to 240 IU/kg/month due to discrete neurological progression. Other aspects of disease, however, showed a significant improvement: decreased visceromegaly and compensatory growth spurt. At six years of age routine pulmonary function testing revealed moderately reduced forced expiratory volume in the first second, but without any clinical signs of lung disease. Chest radiography revealed fine reticulonodular pattern of involvement in lung interstitium. Six months later high resolution computerized tomography (HRCT) of the lungs showed marked bilateral interstitial markings with ground-glass appearance (Figure 1). Fiberoptic bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial biopsy of lung parenchyma were performed. Numerous Gaucher cells were identified in BAL fluid (Figure 2). Histopathology of transbronchial biopsy re-

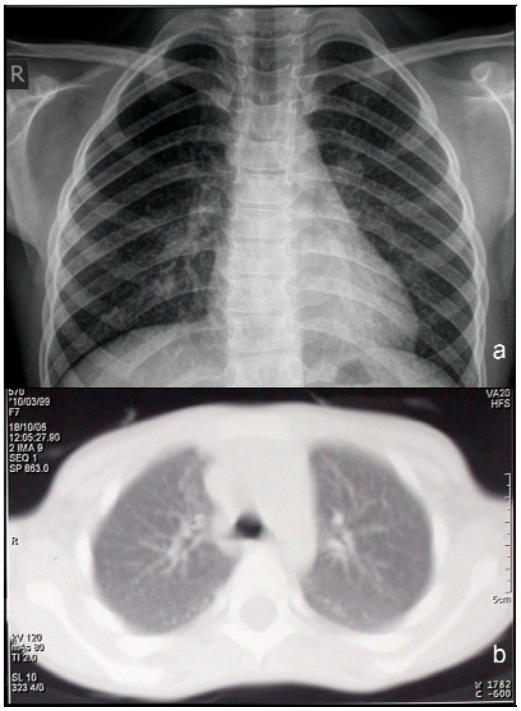

Fig. 1 – a) Chest radiography revealing fine reticulonodular pattern of lung interstitium involvement; b) High resolution computerized tomography of the lungs showing marked bilateral interstitial markings with ground-glass appearance

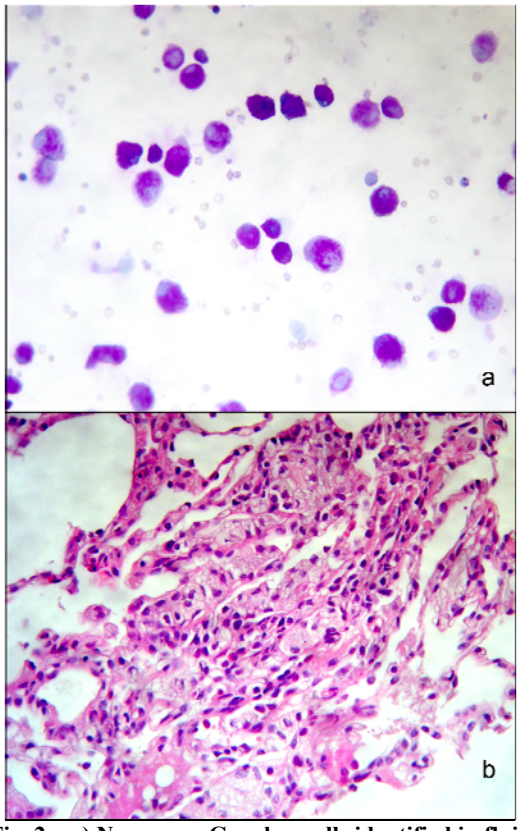

Fig. 2 – a) Numerous Gaucher cells identified in fluid recovered by bronchoalveolar lavage (HE, ×400); b) Histopathology shows infiltration of lung interstitium and alveolar spaces by Gaucher cells (PAS, ×200).

vealed infiltration of lung interstitium and alveolar spaces by Gaucher cells. Eighteen months later there were no significant changes in pulmonary function testing, while a control HRCT three years after baseline evaluation, showed no progression in pulmonary changes. Regular echocardiographic exams showed no signs of pulmonary hypertension. The patient remained without respiratory symptoms during a follow-up period.

Discussion

In the case of two siblings with GD intrinsic lung involvement several issues previously debated in the literature came to light. Genotype and phenotype correlation in GD, with rare exceptions, seems to be rather vague [8–10]. However, several articles pointed out that pulmonary involvement appeared significantly more frequent in patients homoallelic for L444P mutation than in those with other common genotypes [3, 5]. The vast majority (90%) of reported pediatric cases with homozygosity for L444P mutation and lung involvement were diagnosed with GD type III [3, 5]. Our patient J.K. was a homozygote for L444P, and her sister was not genetically tested. A study on variability in phenotype among siblings with GD revealed that in only 4% of families affected members had different genotypes [11]. The same study showed substantial discordance between sibs regarding severity of disease, but there was no available data about pulmonary involvement in these patients.

Another aspect of comparison between these two sisters includes possible effects of enzyme replacement therapy. First child died at the age of 3 years and 4 months with frank interstitial lung disease and progressive respiratory failure, while her sister started receiving ERT at 4 years and 2 months of age with no clinical or radiological signs of pulmonary involvement at the time. Visceromegaly significantly subsided before lung involvement was proven in J.K., while in K.K. the enlargement of abdominal organs most probably contributed substantially to respiratory failure. The presence of chest radiography, HRCT and pulmonary function test abnormalities in J.K. was noted after two and a half years of ERT and several months after the dosage of imiglucerase was increased to 240 IU/kg/month. In J.K. no echocardiographic signs of increased tricuspid incompetence gradient nor signs of pulmonary hypertension on chest X-ray were found. There have been reports that ERT induced pulmonary hypertension in a number of patients [12, 13]. However, a recent study on a large group of children with non-neuronopathic GD did not show substantial incidence of pulmonary hypertension during ERT [14]. Other reports imply that some improvement of pulmonary function and HRCT findings could be expected in children on high dosage ERT [3, 7, 15].

The presence of Gaucher cells in J.K.'s BAL fluid and transbronchial biopsy histopathology confirmed diagnosis of pulmonary involvement in GD. Several previous studies pointed out the significance of BAL fluid citology in diagnosing lung complications of GD and other inborn errors of metabolism [16, 17].

Conclusion

Primary lung disease in children homoallelic for L444P mutation in GBA gene has emerged as a significant clinical manifestation of GD with unclear response to enzyme replacement therapy. Correlation of genotype and phenotype regarding lung disease could be less variable in comparison with other features of GD. Siblings with GD type III reported herein had differencies in progression of lung disease that could be related to ERT.

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