CASE REPORT

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.

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...
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 child 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 \(\beta\)-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 revealed 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 revealed numerous Gaucher cells identified in fluid recovered by bronchoalveolar lavage (HE, \(\times400\)); histopathology shows infiltration of lung interstitium and alveolar spaces by Gaucher cells (PAS, \(\times200\)).
revealed infiltration of lung interstitium and alveolar spaces by Gaucher cells. Eighteen months later there were no signifi-
cant changes in pulmonary function testing, while a control
HRCT three years after baseline evaluation, showed no pro-
gression in pulmonary changes. Regular echocardiographic
exams showed no signs of pulmonary hypertension. The pa-
tient remained without respiratory symptoms during a fol-
low-up period.

Discussion

In the case of two siblings with GD intrinsic lung in-
volvement several issues previously debated in the litera-
ture 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 ap-
peared 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 ho-
mozygosity for L444P mutation and lung involvement were
diagnosed with GD type III 3,5. Our patient J.K. was a homo-
zygote 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 pul-
monary 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 ab-
normalities 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 echocardi-
ographic 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 hyper-
tension during ERT 14. Other reports imply that some im-
provement 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 diag-
nosing 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 re-
placement 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 differences in progression of lung disease that
could be related to ERT.

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