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Case Report

Tuberculosis Revealing Niemann Pick Disease Type B in a Teenager

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Abstract

Introduction: Niemann-Pick disease type A and B are lysosomal storage diseases, caused by a deficiency in acid sphingomyelinase, an enzyme encoded by SMPD1. We report a case of a teenager, who presented an interstitial lung disease with hepatosplenomegaly and diagnosed firstly with miliary tuberculosis then with Niemann pick disease type B.

Case Report: A 14-year-old boy, first born to non-consanguineous parents that were healthy, was brought to us with complains of exertional dyspnea since 2 months. Physical examination showed normal weight and height for age, enlarged spleen and liver, pulmonary auscultation was normal. Chest X-ray showed bilateral interstitial opacities. Thoracoabdominal CT scan revealed bilateral diffuse regular septal thickening with pulmonary micronodules and enlarged spleen with focal calcified granulomas. Tuberculosis screening revealed a positive IGRA, then anti tuberculosis drugs were initiated. Radiological control two months after showed no improvement. Then a lysosomal storage disease was suspected, Enzyme assay for acid sphingomyelinase activity were performed and confirmed the diagnosis of NPD.

Conclusion: ASMD must be considered in the presence of any chronic hepatosplenomegaly and/or interstitial lung disease, to avoid diagnosis delay, and ensure adequate support for those patients.

Keywords: *Niemann Pick Disease Type B; Interstitial Lung Disease; Tuberculosis*

Introduction

Acid sphingomyelinase deficiency (ASMD), commonly known as Niemann-Pick disease (NPD) types A and B, is a rare lysosomal storage disease caused by mutations in the sphingomyelin phosphodiesterase-1 gene on 11p15.4 that encodes for the acid sphingomyelinase (ASM) enzyme and subsequent accumulation of sphingomyelin and other lipids in cells of affected patients [1].

Type A NPD is an infantile, neurovisceral and fatal form of the disorder characterized by massive hepatosplenomegaly and rapidly progressive neurological deterioration [2,3]. Type B NPD is a purely visceral form, with patients surviving until adulthood [1]. Intermediate phenotypes have been also described, in general clinical presentation is related to the amount of residual *in vivo* ASM activity [4,5].

The diagnosis is often delayed by months to years because the complex signs and symptoms overlap with other disorders, creating a diagnostic dilemma for many practitioners.

We report here a case of a 14-year-old child, who presented an interstitial lung disease with hepatosplenomegaly and diagnosed firstly with miliary tuberculosis then with Niemann pick disease type B.

Case Report

A 14-year-old boy first born to non-consanguineous parents that were healthy, was brought to us with complains of exertional dyspnea since 2 months. His growth was normal, and there was no history of recurrent respiratory infections or tuberculosis contagion, but he reported a chronic snoring and asthenia since 2 years. Family history did not involve similar cases in siblings.

Physical examination showed normal weight (52 Kg) and height (168 cm) for age, enlarged spleen and liver, pulmonary auscultation was normal.

Chest X-ray (Figure 1) showed bilateral interstitial opacities, abdominal ultrasound confirmed hepatomegaly and splenomegaly. Thoracoabdominal CT scan revealed bilateral diffuse regular septal thickening with pulmonary micronodules (Figure 2), some of which are calcified, and enlarged spleen (22*7 cm) with focal calcified granulomas (Figure 3). Nasofibroscopy performed for chronic snoring was normal.

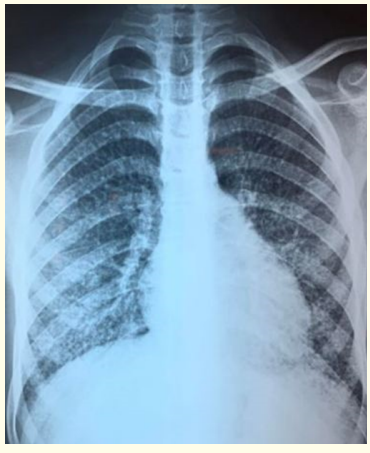

Figure 1: *Chest X-Ray showing an interstitial lung disease.*

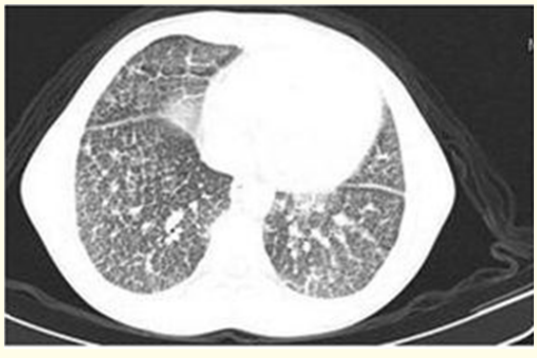

Figure 2: *Thoracic CT scan showing a diffuse interstitial syndrome consisting of diffuse thickening of the septal and non septal lines associated with intra-parenchymal micronodules.*

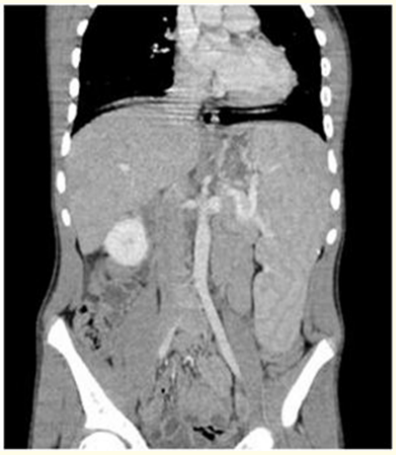

Figure 3: *Abdominal CT scan showing a splenomegaly.*

Hemoglobin (HB), white blood cells (WBC), platelets (P), C-reactive protein and erythrocyte sedimentation rate were within the normal range (HB: 15 g/dl; WBC: 5918/mm^3; P: 157000/mm^3, CRP: 4 mg/l, ESR: 3 mm/h). The parameters for liver function were normal.

Given the endemic situation in Morocco, tuberculosis was the first diagnosis to rule out in front of an interstitial lung disease. Tuberculosis screening revealed a positive IGRA test (0.4 UI/ml [< 0.35]), with negative sputum GENEXPERT MTB/RIF. Then anti tuberculosis drugs were initiated according to the regimen 2RHZE/10RH, which is miliary tuberculosis regimen.

The evolution two months later showed an improvement of the dyspnea, but hepatosplenomegaly were persistent and control chest x-ray showed no radiological cleaning.

Then, given interstitial pulmonary disease, hepatosplenomegaly and history of chronic asthenia since 2 years, analysis for metabolic disease were performed for lipidic storage disease. We started with lipidic profile which showed a mildly decreased HDL cholesterol (0.37 g/l) with normal LDL cholesterol (LDL: 1.15 g/l). Eye examination was normal and Fundus did not show cherry red spot.

Enzyme assay for acid sphingomyelinase activity and glucocerebrosidase activity (for Gaucher disease) were performed and confirmed the diagnosis of NPD (normal glucocerebrosidase activity and low ASM activity (0.5 µmol/h [> 1.2]).

Since there is no treatment for Niemannpick disease, the patient was managed with a low-fat diet and monitoring of his respiratory function, platelet and hemoglobin levels and lipidic profile.

Discussion

Niemann-Pick disease is a rare lysosomal storage disease in which sphingolipids accumulate in reticuloendothelial cells due to acid sphingomyelinase deficiency. Although all patients with ASMD share the same basic metabolic defect, a spectrum of clinical presentations and outcomes results from differences in disease severity, which contribute to the diagnostic challenges [6].

In Type B or chronic visceral ASMD, Lipid storage is slow and progressive and leads to deterioration in multiple organ, being most commonly deposited in the liver, spleen, lymph nodes, adrenal cortex and lungs [7]. It is characterized by a variable age of onset ranging from infancy to adulthood [8].

For our patient diagnosis has been done in adolescence following the tuberculosis infection, otherwise the diagnosis could have been delayed.

The most common initial manifestation of type B NPD is hepatosplenomegaly, which is usually noticed during early childhood, although mild disease may not be diagnosed until adulthood [9]. Children with type B NPD often have growth restriction, particularly of linear growth, which is associated with a delayed bone age. Delayed onset of puberty, often by several years, is common [10]. Other common disease manifestations include fatigue, bone and joint pain, osteopenia, thrombocytopenia and leucopenia.

Pulmonary function may worsen over time, and interstitial lung disease and pulmonary infections are common [11].

Interstitial lung disease was found in 90 - 98% of Niemann pick B patients according to a multi-center study in which 53 NPD-B patients were examined prospectively [12].

There also may be a reddish-brown halo surrounding the macula in the eyes of these patients, and in some cases a distinct cherry red spot can be identified [13]. Lipid profiles are typically characterized by increased LDL cholesterol, VLDL cholesterol, and triglyceride levels, whereas HDL cholesterol levels are substantially decreased [14].

When ASMD is suspected an enzyme assay for ASM activity should always be performed first, with gene sequencing to follow once the biochemical diagnosis has been confirmed [6]. To date, more than 180 mutations have been found within the SMPD1 gene causing types A and B NPD [13].

For our patient following clinical features and lipidic profile (mildly decreased HDL cholesterol) an assay for glucocerebrosidase activity was simultaneously performed to rule out Gaucher disease. Gene sequencing was not performed given the socio-economic level of the patient.

Although there is no effective treatment for Type B, limited success has been achieved in the small number of patients who underwent bone marrow and stem cell transplantation [15]. Enzyme Replacement Therapy (ERT). The gold standard of achieving widespread enzyme delivery to organs of pathology in NPD is under development [13].

Conclusion

Patients with ASMD present with a large phenotypic spectrum of nonspecific disease manifestations that can lead to considerable diagnostic delay and missed cases. To avoid this diagnostic delay, ASMD must be considered in the presence of any hepatosplenomegaly or interstitial lung disease with negative etiological assessment.

Conflicts of Interest

The authors declare that they have no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Informed Consent

Informed consent has been obtained from the patient's parents for publication of the case report.

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