

Case Report

Farber disease: report of three cases with joint involvement mimicking juvenile idiopathic arthritis

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Abstract

Farber disease is a rare recessive autosomal disorder presented with three main features of joint involvement, subcutaneous nodules and hoarseness. Hereby we describe three new cases of Farber disease. All three cases were first misdiagnosed as juvenile idiopathic arthritis (JIA) due to the presentation of joint swelling. Addition of hoarseness and subcutaneous nodules to the initial joint swelling questioned the diagnosis of JIA and further evaluations led to the diagnosis of Farber disease. The first case was a 4-year old girl in whom a novel genetic mutation in *ASAH1* gene was found. The second patient was a 4-year old girl presented with joint swelling at 7 month of age. The third patient was a 9-month boy complicated with severe respiratory distress. All patients were treated with symptomatic and supportive care. Two cases died due to respiratory failure and infection, but one patient follow up for 2 years after diagnosis. Farber disease should be considered as differential diagnosis in children with early onset of poly articular involvement with subcutaneous nodules and/or hoarseness.

Keywords: Farber Disease, Subcutaneous Nodules, Hoarseness, Juvenile Idiopathic Arthritis

Background

Lysosomal storage disorders comprise a wide variety of diseases with over 50 distinct disorders. Farber disease (lipogranulomatosis) is a rare lysosomal storage disorder which was first introduced by Farber in 1952¹. In his report, this disease had features intermediate between Histiocytosis (Hand-Schuller-Christian) and a lipid storage disease (Niemann Pick disease). Several years later, it was discovered that the stored lipid was ceramide and the deficient enzyme was ceramidase^{2,3}. Acid ceramidase (N-acyl sphingosine Amidohydrolase) is involved in degradation of ceramide into fatty acids and sphingosine. Deficiency or low activity of acid ceramidase leads to the accumulation of ceramide in various

tissues of the body⁴. This disease is mainly characterized by a clinical triad: Joint involvement, appearance of subcutaneous nodules ordinarily near or over the joints and laryngeal involvement which leads to progressive hoarseness. There are wide variations in the clinical manifestations which was resulted in a 7-phenotype classification of Farber disease⁵. The onset of disease is usually within the first year of life and life span does not exceed 3-4 years but longer lives are expected in patients without severe neurologic involvements. Up to now, less than 100 cases of Farber disease are reported in the literature. Hereby we describe three new cases of Farber disease.

Case presentation

1st case

This patient was a 4-year old girl, second child of related parents, delivered by cesarean section without any insult.

This child developed wrist swelling at 6 months of age. Swelling of other joints were gradually added. On examination, swelling and limitation in range of motion was detected in PIP, MCP, wrist, elbow and shoulder joints of upper limbs and PIP, MTP, tarsal joints and ankle in lower limbs.

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Figure 1. a) swelling in the knee in case 2 at the age of 2 years. b) Multiple nodules on extensor surface of hands in case 2 at the age of 2 years. c) Nodular masses within lumbar regions on the spine at 4 years.

Multiple firm subcutaneous nodules were found on joints –mainly on extensor surfaces- which led to deformation of joint, tenderness and inability to walk. Contracture in joints was evident in physical examination. Progressive hoarseness was present. Reports of head drop attacks were found in the history. In neurologic examination, deep tendon reflexes were diminished or absent. Although cognitive function of this patient was normal, motor and speech development was delayed. Two years later, development of seizure and tremor was reported. Tremor was evident in all limbs on physical examination. Laboratory serologic tests were normal.

Radiography of both hands showed reduction in density of bones, swelling of both wrists, deformity of wrist bones, marginal erosion of wrist bones and distal phalanges in PIP and DIP joints which all were suggestive of advanced juvenile idiopathic arthritis (JIA). Chest X-ray also showed alveolar opacities with air bronchogram in the upper lobe of right lung which were in favor of pneumonia. Bronchoscopy showed a circular contraction in subglottic region of larynx.

After development of neurologic involvements, Farber disease was suspected. To confirm the diagnostic suspicion, genetic analysis was performed. *ASA1* gene analysis – gene related to Farber syndrome- revealed a homozygous variant which confirmed the presence of Farber disease in this patient. This variant was a novel mutation in exon 8 of *ASA1* gene (c.553T>C p.Trp185Arg).

Patient had not received treatment till the age of 2.5 years. After she was diagnosed with JIA, methotrexate, hydroxychloroquine, prednisolone and infliximab medications were initiated. After genetic testing and establishment of the diagnosis of Farber disease, patient's treatment was switched to cyclosporine and prednisolone. With the development of neurologic involvements, Topiramate, valproate sodium and clobazam was prescribed for relieving debilitating neurologic symptoms. Bone marrow transplantation was suggested as a treatment strategy for the patient but the suggestion was declined by the family. She has under follow up after 2.5 years with neurological deficit.

2nd case

This patient was a 4 year-old girl, first child of a non-related couple, delivered by NVD who was term on birth.

The patient developed swelling of joints at 7 months of age. Particularly in PIP and MCP joints, wrists and ankles (Figure 1a). On examination at the age of 2 years, she had multiple subcutaneous nodules on head, hands and chest (Figure 1b). Progressive hoarseness was also present. Extensive mucosal lesions were detected in the oral cavity. Limitation in knee's range of motion was severe leading to difficulty in walking. Cutaneous lesions were also seen on abdomen. In the follow-up after two years, patient had developed nasal swelling. On examination, three relatively soft masses were found within lumbar to coccygeal regions of the spine with diameters of up to 5 centimeters (Figure 1c). Muscular atrophy of all four limbs and gluteal region was evident. In the auscultation of the lungs, wheezing was detected. Joints' examination showed nodules and range of motion limitation in both

elbows, shoulders, MCPs, PIPs and DIPs in upper limbs. In lower limbs, knees and ankles were affected with contracture, nodules and range of motion limitation.

In radiography, bilateral destruction of proximal humerus and severe osteopenia were seen. After a while, progression of hoarseness and development of multiple percutaneous nodules put the diagnosis of JIA under question. Biopsies were taken from nodules to rule out Farber disease. Histopathologic examination reported collection of collagen bundles and foamy macrophages which were suggestive of Farber disease.

With the early diagnosis of JIA, the patient underwent treatment with folic acid, prednisolone, cyclosporine, ibuprofen, calcium supplement and nystatin. MTX was initiated for the patient but then was discontinued due to the appearance of cutaneous lesions on the body. Corticosteroid pulses and Etanercept injections were also prescribed. Subcutaneous nodules increased gradually and she was admitted 4 times due to respiratory distress. Finally she died from respiratory failure in one episode at 4 years old.

3rd case

This patient was a 9-month old boy, the first child of related parents who was delivered by NVD without any insult. Rheumatoid arthritis history was positive for patient's father.

The patient was presented to the clinic at 9 months of age with one month history of left wrist swelling and tenderness. Within one week prior to the presentation, swelling had extended to the dorsal surfaces of the hands. Patient had been misdiagnosed with JIA and treatment with Prednisolone, MTX and ibuprofen was started.

Hoarseness had developed 6 months earlier. Weight loss was also reported. On examination, lower limbs were normal but in upper limbs, limitations in flexion and extension of wrist and swelling of fingers were noted. Patient was presented to the clinic again at 18 months of age with delayed motor development, multiple subcutaneous nodules in wrists and ankles, respiratory distress and hoarseness (Figure 2).

In bronchoscopy, large cysts on vocal cords were seen. On radiography, osteopenia was evident (bone age equal to 9 months at the age of 18 months). CXR visualized bilateral perihilar opacities and hyperinflation in both lungs. In kidney, contrast opacity resembling kidney stone was seen. HPLC was normal. Laryngeal nodules led to severe respiratory distress which his life ended after ICU admission and tracheostomy insertion.

Discussion

Farber disease as a rare lysosomal storage disease has so few reports in the literature and we aimed to add to the present knowledge on this disease. Our patients showed clinical triad of Farber disease in addition to neurologic involvements. According to the classification of Farber disease phenotypes, our patients can be categorized as type 1 disease. In type 1, classic form of the disease with subcutaneous nodules,



Figure 2. Multiple nodules on extensor surface of hands in case 3 at the age of 18 months.

hoarseness and joint involvement is always seen and progressive neurologic involvement and lung diseases are reported in many cases. Presence of typical clinical triad in type 1 patients confirms the diagnosis without the need for any further evaluations⁶. In patients without clinical triad of Farber disease, diagnosis of Farber disease is based on measuring acid ceramidase activity in lysosomes of cultured skin fibroblasts and leukocytes or performing a ceramide loading test in fibroblasts. Not only in homozygotes but also in heterozygote patients, reduction of acid ceramidase activity is seen. Biopsy of involved tissues particularly percutaneous nodules is a robust basis for the diagnosis. In cases of prenatal suspicion of Farber disease, measurement of acid ceramidase in amniotic fluid cells is diagnostic^{4,5}. Genetic analysis also contributes to the diagnosis. ASA1 gene is identified to be associated with Farber disease. It is of note that mutations leading to spinal muscular atrophy with progressive myoclonic epilepsy are originated from the same gene⁷. A review reported that 45% of identified mutations in Farber disease patients were located in ASA1 exon 6-10⁸. To date, about 20 mutations in this gene for Farber disease are described. In one our patients, a novel mutation was found in exon 8 of ASA1 gene (c.553T>C p.Trp185Arg) which was not previously reported.

Our patients were misdiagnosed as JIA in the first presentation. One of the most challenging diagnostic issues is the similarity of Farber disease and JIA. Mainly mild cases of Farber disease without neurologic involvement are misdiagnosed as JIA. In Farber disease large and small joints are affected with bilateral symmetric pattern

similar polyarticular JIA. Our patients had polyarticular involvement pattern.

Onset of disease in Farber disease is within the first year of life while in JIA onset of under 1 year of age is unusual. Presence of subcutaneous nodules is associated with Farber disease. Joint pain is the cardinal symptom of Farber disease while severe joint pain in children is not usual in JIA. Hoarse voice, splenomegaly and hepatomegaly are not present in JIA and suggest Farber disease diagnosis. These clinical clues must be taken into consideration when making a diagnosis⁹.

The final outcome of patients is usually death due to severe respiratory infection/distress within the several first years of life⁵. The classic form of Farber disease begins at 3-6 month age and leads to death in 2 years of age. Mild forms of Farber disease live longer up to 7 years of age and lack neurologic deficits. Higher ages might be seen in milder forms¹⁰. In this report, final outcome of 2 cases was death due to respiratory failure, but one girl patients is under follow up after 2 years with neurological deficit.

Some enzyme replacement treatments are being developed in the research scale. A recombinant acid ceramidase has been synthesized and tested in preclinical experiments¹¹. Animal studies showed that mice with acid ceramidase deficiency benefit from the injection of human acid ceramidase-encoding lentivector. This treatment led to a considerable decrease in severity of the disease¹². Theoretically, enzyme substitution can relieve symptoms of Farber disease¹³ but there is no definitive treatment for the disease at this time. Hematopoietic stem cell transplantation (HSCT) leads to remarkable improvement in cases with no neurologic involvement⁶. HSCT has been suggested to improve global function and peripheral manifestations of the disease such as hoarseness and joints' involvement. HSCT has not been proved to be effective in preventing neurologic impairments¹⁴. This treatment is limited by the availability of suitable donors and significant associated risks. A case report on Farber disease in infancy reported that two months after BMT, the subcutaneous nodules greatly decreased in size and the number of joints with limited motion decreased significantly leading to a dramatic improvement in motor activity. His hoarseness has completely resolved. Inflammatory markers grew normal in regular checks. Growth and development in different aspects of cognition and neurology was pursued¹⁵. The study concluded that the results of BMT are in favor of the curative effect of HSCT in Farber disease without neurologic and cognitive impairments. To reach an ideal outcome, early diagnosis and treatment are vital. Joint therapeutic strategies of enzymatic therapy and medications for alterations in ceramide metabolism are promising paths for the future of treatment in Farber disease¹⁶.

Genetic study was performed in one patients and she has a novel mutation. Absence of genetic study in 2 other patients and absence of extensive familial carrier testing to clarify the significance of this variant in the first case, were the most important limitations of this study.

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