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CASE REPORT
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Ichthyosis and ARSA deficiency: An unusual clinical presentation

İktiyozis ve ARSA eksikliği: Farklı bir klinik sunum

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Öz

Metakromatik lökodistrofi (MLD), arilsülfataz A (ARSA) eksikliğinden kaynaklanan nadir bir çocukluk çağı hastalığıdır. Sülfatidlerin depolanması merkezi sinir sisteminde dismiyelinizasyona neden olur ve bu da klinik olarak nörodejeneratif bir süreçle sonuçlanır. Multipl sülfataz eksikliği (MSD) ve steroid sülfataz eksikliğinde iktiyoz görülebilir ancak arilsülfataz eksikliği ile birlikte iktiyoz daha önce tanımlanmamıştır. Burada iktiyozlu geç infantil metakromatik lökodistrofi tanısı alan ve ARSA gen analizinde homozigot mutasyon (c.619G>C) saptanan bir olguyu sunuyoruz. Bildiğimiz kadarıyla ARSA eksikliği ile birlikte iktizozis daha önce bildirilmemiştir.

Anahtar kelimeler: Metakromatik lökodistrofi, ARSA, iktiyozis

Abstract

Metachromatic leukodystrophy (MLD) is a rare childhood disease caused by arylsulfatase A (ARSA) deficiency. Storage of sulfatides leads to dysmyelination in the central nervous system, resulting in a clinically neurodegenerative process. Ichthyosis can be seen in multiple sulfatase deficiency (MSD) and steroid sulfatase deficiency, but ichthyosis with arylsulfatase deficiency has not been defined. Herein, we present an individual diagnosed with late infantile metachromatic leukodystrophy with ichthyosis and ARSA gene analysis revealed a homozygous mutation c.619G>C (p.Ala207Pro). To our knowledge, ichthysosis with ARSA deficiency has not been reported previously.

Keywords: Metachromatic leukodystrophy, ichthyosis, ARSA

Introduction

Metachromatic leukodystrophy (MLD) is an autosomal recessive inherited leukodystrophy and the late infantile form is the most common form with a range of % 50-80 [1-2]. Metachromatic leukodystrophy results from a deficiency of the enzyme ARSA, whose gene is located on chromosome 22q13, which leads to the accumulation of 3-O-sulfogalactosylceramide (sulfatide) in various organs, including Schwann cells, oligodendrocytes and neurons, impairing myelination and function.

Clinical manifestations of the late infantile form of MLD usually include developmental delay, gait abnormalities, muscle wasting, weakness, muscle

stiffness, progressive vision loss, swallowing difficulties and seizures [2,3].

Ichthyosis is due to abnormal epidermal differentiation or metabolism. The most common cutaneous findings are polygonal, dark, adherent and regular scales and generalised dryness of the skin. Multiple sulfatase deficiency (MSD) ichthyosis is caused by a deficiency of steroid sulfatase (arylsulfatase C). Isolated steroid sulfatase deficiency is responsible for X-linked ichthyosis. Other deficiencies of different sulfatases (arysulfatase B, iduronate sulfatase) cause features of mucopolysaccharidosis such as organomegaly, gross facial and skeletal abnormalities. The association between ARSA deficiency and ichthyosis is unknown and in this case we aimed to evaluate the association between ARSA deficiency and ichthyosis.

Case report

The individual of Syrian origin was born by spontaneous normal delivery at 39 weeks' gestation. She was the first daughter of healthy first cousins and her younger sister and brother were healthy (aged 5 and 3 years). Her developmental milestones were delayed but she continued to make progress; at 4 months of age the individual was able to hold her head up and at 14 months she was able to sit unsupported, at 2 years of age she had a series of single words, was pulling to stand but not walking. Over the next few months her cognitive and motor skills declined.

She was treated for pulmonary tuberculosis 2 years ago and had several hospital admissions. She was admitted to the paediatric intensive care unit for respiratory failure. She had feeding difficulties, so a nasogastric tube was placed and enteral nutrition was started. She was diagnosed with ichthyosis vulgaris and topical vaseline therapy 500 mg 3 times a day was recommended by the dermatology clinic, but the parents did not comply with the treatment.

On physical examination she had generalised axial hypotonia and muscle weakness. Her deep tendon reflexes were depressed. She had spastic tetraparesis. There was no hepatosplenomegaly or skeletal abnormalities. She had loss of vision, cognitive and motor functions. She had hyperkeratosis of the scalp, face, trunk and extremities compatible with ichthyosis, which had been present since early infancy (Figure 2). Her weight was 9.25 kg and her height was 85 cm. (Weight SDS was - 5.5 and height SDS was - 5.44) She had a history of generalised tonic-clonic seizures and was treated with phenobarbital 5 mg/kg/day. Under phenobarbital treatment she had prolonged generalised tonic-clonic seizures. She was admitted to the paediatric intensive care unit with a diagnosis of status epilepticus, started on intravenous phenytoin 20 mg/kg and levetiracetam 20 mg/kg, and the status epilepticus was terminated. Levetiracetam 40 mg/kg/day and phenytoin 5 mg/kg/day were added for maintenance. Electroencephalography showed no epileptic pattern with immature basal activity. MR imaging revealed widespread symmetrical demyelination of the central and periventricular white matter with sparing of the subcortical U-fibers and a tigroid pattern of white matter involvement at the level of the centrum semioval (Fig. 1a). ARSA gene analysis revealed a base pair substitution at position c.619G>C (p.Ala207Pro) in exon 3.

She had tachycardia, electrocardiography showed sinus tachycardia and echocardiography showed patent foramen oval, she was treated with propranolol.

She was referred to the dermatology clinic for extensive erythroderma and hyperkeratosis. A punch biopsy was performed and treatment with intravenous metilprednisolone (0.5 mg/kg/day) was started for 5 days and continued with topical steroids. Punch biopsy showed orthokeratotic hyperkeratosis on the surface in sections, pustule formation in the keratin layer, focal mild hypogranulosis in the epidermis, pronounced acanthosis spongiosis, neutrophil exocytosis, tiny pustule formations, mostly interstitial mononuclear infiltration with sparse neutrophils in the superficial dermis. The patient responded very well to systemic steroid therapy. Topical antifungal therapy was started for the genital area, topical steroid therapy for the body was discontinued and moisturizing treatment was continued.

Because of the ichthyosis, other sulfatase enzyme activities for multiple sulfatase deficiency and mucopolysaccharides were within the normal range. She underwent fundoplication and gastrostomy for dysphagia. She was tetraplegic and in a vegetative state. Her seizures were controlled with phenobarbital, levetiracetam and phenytoin. She died of respiratory failure at the age of 6.5 years.

We have obtained the patient consent form from the parents.

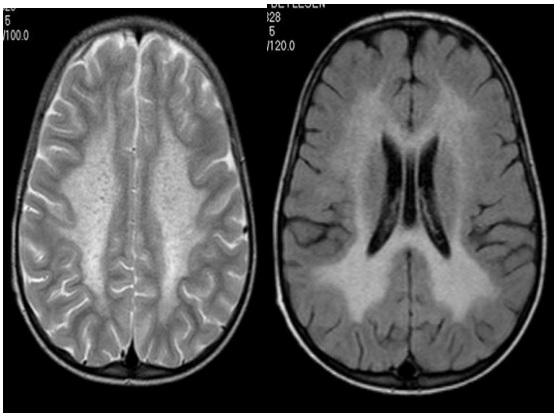

Figure 1. Leukodystrophy with periventricular perivenular sparing ‘tigroid pattern

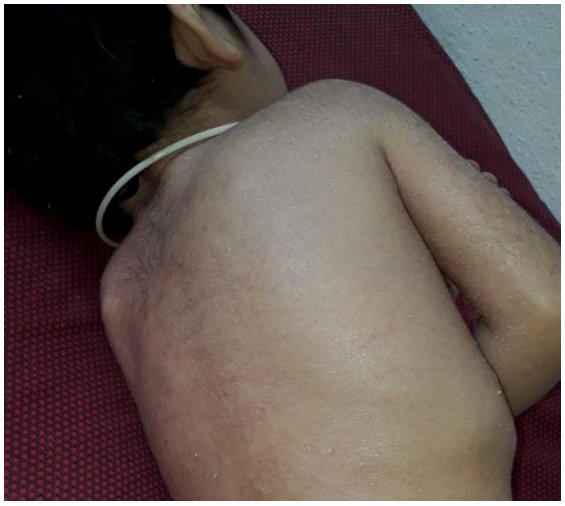

Figure 2. She had hyperkeratosis with the diagnose of ichthyosis

Discussion

MLD is a progressive neurodegenerative disease and there is no defined enzymatic or genetic treatment to prevent neurodegeneration. Supportive treatment with antiepileptic drugs for seizures and muscle relaxants for contractures should be considered. A number of developing treatment options for MLD have been tested, but these therapies remain controversial and effectiveness has not been proven [1,4].

ARSA deficiency causes neurological symptoms due to the accumulation of sulfatides in Schwann cells, oligodendrocytes and neurons. Accumulation of steroid sulfatases in the skin results in ichthyosis. Ichthyosis can also be seen in multiple sulfatase deficiency (MSD), which can be misdiagnosed as metachromatic leukodystrophy (MLD) due to similar neurological and neuroimaging findings.

X-linked recessive ichthyosis is a common form of ichthyosis caused by steroid sulfatase deficiency and affects 1/2000-6000 males. We didn't test for steroid sulfatase deficiency because of the sex of the individual. In the literature, a 4-year-old boy with mild ichthyosis and neurological deterioration suggested the diagnosis of metachromatic leukodystrophy with reduced leukocyte arylsulfatase A activity and prominent steroid sulfatase deficiency, but there was no genetic result to support the diagnosis of MLD [5].

MSD may overlap with arylsulfatase A deficiency. MSD can have very low ARSA enzyme activity, deficiency of most sulfatases and cause MLD like clinical manifestations, skeletal abnormalities and ichthyosis. In our case she had a normal range of other sulfatase enzyme activities and there were no skeletal abnormalities.

Multiple sulfatase deficiency is caused by mutations in the SUMF1 gene [6], but we were unable to perform SUMF1 gene analysis Also the genes responsible for the etiology of ichthyosis have not been analyzed in our case. Steroid sulfatase deficiency can cause ichthyosis, but there aren't any cases of congenital ichthyosis with arylsufatase A deficiency diagnosed as metachromatic leukodystrophy. Sulfatide accumulation can be seen in various organs, especially in the central nervous system, but there is no knowledge of dermatological accumulation. To our knowledge, this is the first case of late infantile metachromatic leukodystrophy diagnosed with congenital ichthyosis.

The wide range of clinical manifestations and biochemical abnormalities suggests that complex mechanisms are critical to the heterogeneity of MLD. The ARSA enzyme mutation for the sulfatase activities that complicate the biochemical process has not yet been identified. The relationship between ichthyosis and factors affecting ARSA enzyme activity is unknown, and other biochemical and epigenetic factors may influence the clinical phenotype of MLD.

In conclusion, the combination of neurological disease and ichthyosis can be defined as neuro-ichthyotic syndromes. Genetic and metabolic investigations are necessary because of the similar clinical findings of MLD and MSD in neuro-ichthyotic syndromes. Ichthysosis with ARSA gene mutation has not been reported and further studies are needed to determine the pathogenesis of ARSA deficiency leading to accumulation of sulfated lipids in the skin.

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