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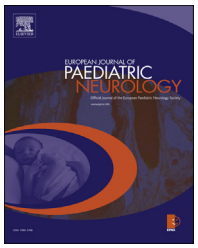

Case study

Late diagnosis of fucosidosis in a child with progressive fixed dystonia, bilateral pallidal lesions and red spots on the skin

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ABSTRACT

Fucosidosis is a rare lysosomal storage disease. A 14-year-old girl is presented, with recurrent infections, progressive dystonic movement disorder and mental retardation with onset in early childhood. The clinical picture was also marked by mild morphologic features, but absent dysostosis multiplex and organomegaly. MRI images at 6.5 years of age were reminiscent of pallidal iron deposition ("eye-of-the-tiger" sign) seen in neurodegeneration with brain iron accumulation (NBIA) disorders. Progressively spreading angiokeratoma corporis diffusum led to the correct diagnosis. This case extends the scope of clinical and neuroradiological manifestations of fucosidosis.

1. Introduction

Fucosidosis (MIM # 230000) is a rare lysosomal storage disorder (LSD), caused by α-L-fucosidase deficiency. α-L-fucosidase is involved in the degradation of fucose-containing glycoproteins and glycolipids. Since the first description of its deficiency in 1966,[1] less than 120 cases have been documented in the literature. Patients present typically with progressive cognitive and motor deterioration, coarse facies, growth

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retardation, recurrent infections, dysostosis multiplex, angiokeratoma corporis diffusum (ACD), visceromegaly and seizures.[2] Thin-layer chromatography of urinary oligosaccharides, a screening test for a number of LSD, shows a suggestive pattern. The diagnosis is confirmed by severely decreased activity of the α-L-fucosidase and/or genetic analysis of the FUCA1 gene on chromosome 1p36.11.

Treatment of fucosidosis is largely supportive. Bone marrow stem cell transplantation was efficient in dogs,[3] but this treatment is not standard in humans so far.[4,5]

Here, we present the case of a 14 year old girl whose peculiarities clouded the natural history of the disease leading to a diagnostic delay of more than 10 years.

2. Case study

The girl of Eritrean descent was the second child of a consanguineous marriage, born normally after an uneventful pregnancy. From two months of age, frequent upper respiratory tract infections were noted. Recurrent gum infections (mainly Candida), and treatment-refractory iron-deficiency anemia became prominent after 2 years of age. Thalassemia was excluded, and extensive immunological investigation was normal apart from a selective immune deficit against Candida ssp on proliferation testing. An endocrinological work-up in search of an auto-immune syndrome was completely normal. Mild dysmorphic features, namely Mongolian eye slant, arcuated eyebrows, and bilateral ptosis, were first noted by 4 years of age (Fig. 1). By that time, psychomotor retardation had progressively become obvious, while neurological examination was considered normal despite a slightly hesitating gait. The skin was described as very dry, and there were blue-brown spots on tongue and sclerae. The tongue was protruding due to macroglossia. After 5 years, slowly progressing muscle weakness and increased tendon reflexes were observed, turning rapidly into a growing generalized hypertonia dominated by dystonic posturing. Unsupported ambulation, acquired at 20 months, became gradually unsteady and was lost soon after her 8th birthday, during a period of considerable motor regression. A baclofen pump was placed at around 10 years to reduce the painful dystonia, which also affected the neck and the facial muscles. Currently, the patient has a complete loss of voluntary movements with a fixed dystonia associated with multilevel joint contractures. Somatic growth slowed down and fell below P3 after age 6 years. For years, recurrent episodes of protracted vomiting prompted frequent calls at the emergency department. Gastrostomy was put in place at 12 years, with only transitory weight gain. There was no organomegaly; fundoscopy was repeatedly normal and conventional radiographs did not show any sign of dysostosis multiplex. At 6.5 years, a brain MRI showed an abnormal signal of the bilateral pallidum (Fig. 2), interpreted at the time as “eye-of-the-tiger”, but the mutation analysis of the PANK2 gene was negative. The MRI was repeated two years later, showing some progression of brain atrophy, but otherwise unchanged findings. At 14 years, the patient was finally consulted by a dermatologist who diagnosed ACD (Fig. 3). Based on this finding and the uncommon association with basal ganglia lesions on MRI, the possibility of fucosidosis was raised simultaneously by a consulted geneticist and the dermatologist. The diagnosis of fucosidosis was confirmed enzymatically in serum and lymphocytes (zero activity of α-L-fucosidase) and genetically (homozygous nonsense mutation in exon 8: c1295G > A p.W432X). This mutation has not been described before.

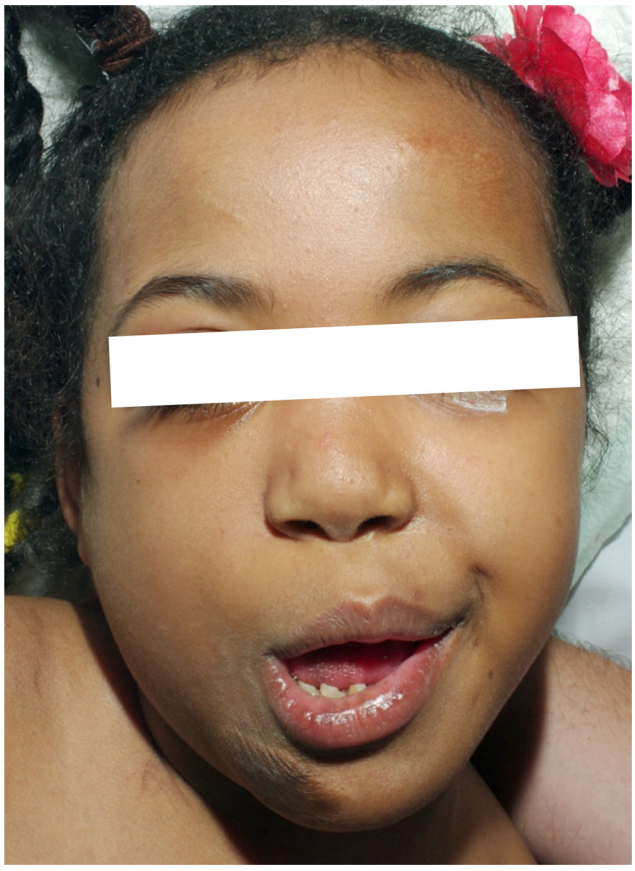

Fig. 1 – Photograph of the patient at age 14 years. Relatively mild morphological features. Note the facial asymmetry, mainly caused by oro-mandibular dystonia. A chin scar consecutive to a burn is also visible.

3. Discussion

Several aspects of this case are instructive and extend the scope of clinical and neuroradiological manifestations of fucosidosis.

The combination of clinical signs was a strong pointer towards a lysosomal origin of the disease very early on in its course. Neurological and developmental degradation combined with recurrent infections, treatment refractory anemia and morphological abnormalities such as unusual facial features, a large protruding tongue and gum hypertrophy, as well as later on, failure to thrive, must prompt the screening for LSD. Coarse facies is reported in 79% of fucosidosis patients.[2] These dysmorphic features are typically very unspecific, even subtle and must not be overlooked (Fig. 1). Dysostosis multiplex and organomegaly were absent in this patient, as in