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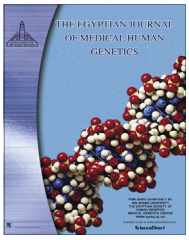

CASE REPORT

Alpha-fucosidosis – Two brothers presenting with dysostosis multiplex

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KEYWORDS

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Abstract α-Fucosidosis is a rare inherited neuro-degenerative disorder causing progressive neurological deterioration leading to early death. Definitive diagnosis requires α-fucosidase enzyme assay or FUCA1 gene testing, which being expensive limits the definitive diagnosis in resource limited countries. We present two siblings with classic symptoms, radiological and MRI brain findings suggestive of α-fucosidosis and a clinical approach to reach to the diagnosis.

1. Introduction

α-Fucosidosis (OMIM # 230000) is an autosomal recessive lysosomal storage disorder caused by the deficiency of fucosidase enzyme due to mutations in *FUCA1* gene [1]. It was first reported in 1966 [2] and since then less than 120 cases have been reported [3]. Patients present with broad clinical spectrum of progressive psychomotor regression, coarse facies, dysostosis multiplex, angio-keratoma, visceromegaly and seizures [4]. The definitive diagnosis of α-fucosidosis is established based on either the decreased activity of fucosidase enzyme or the detection of a mutation in *FUCA1* gene. Both approaches are expensive and often limit the definitive diagnosis in countries with limited resources. We present two siblings with α-fucosidosis from Pakistan, focusing on radiological findings as a diagnostic tool to develop an approach to a patient with dysostosis multiplex, in neuro-degenerative disorders including α-fucosidosis (Fig. 1).

2. Case report

2.1. Patient 1

A 6.5 year old boy, third child of first-cousin parents, was seen at the metabolic clinic for psychomotor regression noted at 11 months of age. He was born after a full-term, uneventful pregnancy. The parents reported normal growth and development till 11 months of age, after which initial stagnation of development followed by progressive spasticity of body was noted. Eventually his ability to sit unsupported and cruise was lost. Parents also reported progressive deterioration in his ability to understand and respond socially. Frequent aspiration during feeding was a significant issue. However, no sei-

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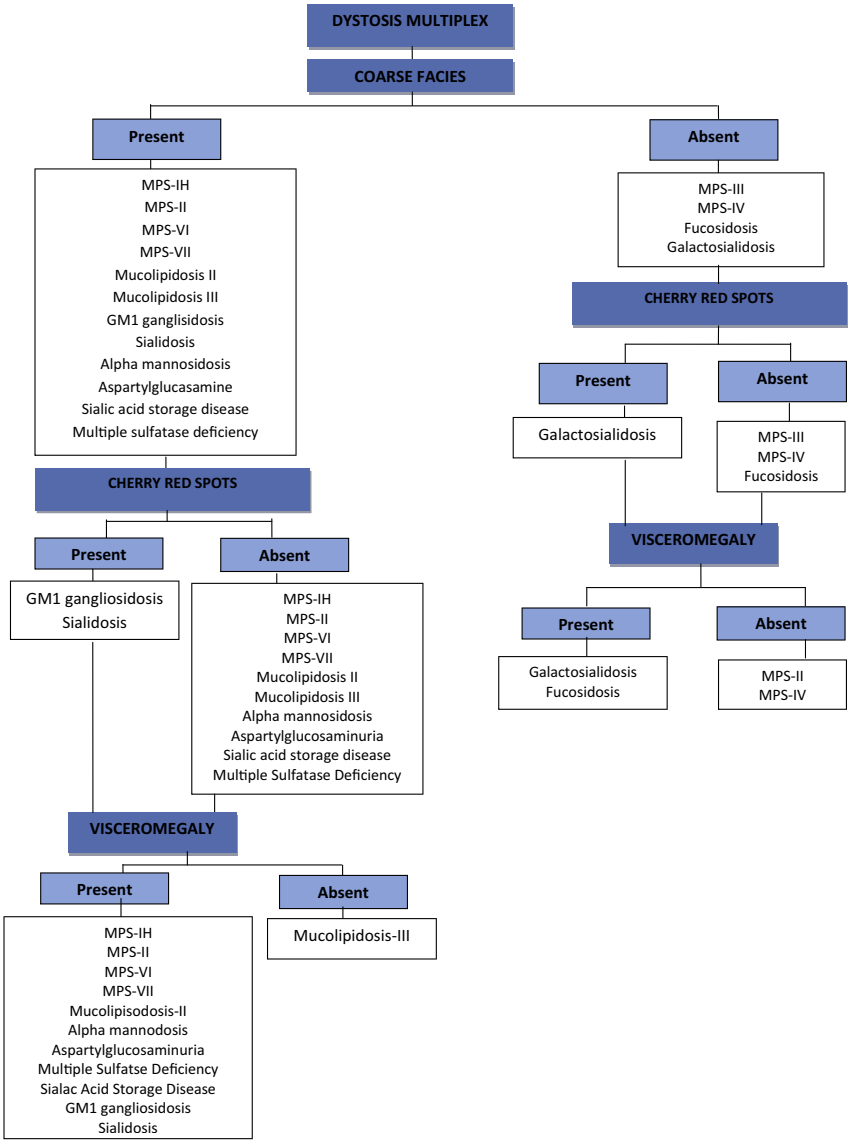

Figure 1 Approach to dysostosis multiplex.

zures were reported. At the time of his assessment weight, height and head circumference was 11 kg, 91 cm and 46.5 cm respectively (all $<$5th percentile). He was noted to have no facial coarsening but a scissoring posture along with hepatosplenomegaly was noted on physical examination; liver was 5 cms below right coastal margin and spleen 3 cms in the long axis, (Fig. 2a). He was also noted to have spastic quadraparesis with increased deep tendon reflexes. However, no corneal clouding, contractures or cutaneous changes including angiokeratoma were noted. Ophthalmologic evaluation did not reveal cherry red spots. X-ray of the spine showed an anterior breaking of lumbar vertebrae, (Fig. 3a). The MRI brain was done, which showed a significant loss of white matter causing cerebral atrophy and enlarging CSF spaces (Fig. 3b).

Based on the clinical features of hepatosplenomegaly, dysostosis multiplex on X-rays, classical MRI brain features along with the absence of facial coarsening and cherry red spots; our differential diagnosis included Alpha-fucosidosis, Mucopolysaccharidosis type III & type IV. In our patients, psychomotor regression and the presence of organomegaly led us to the diagnose Alpha-fucosidosis as Psychomotor regression is not a feature of Mucopolysaccharidosis type IV and organomegaly is not noted in Mucopolysaccharidosis type III and type IV. To evaluate for the cause, his urine oligosaccharide analysis was performed at Institute Medical Research, Kuala Lumpur, which showed densely-staining band at the origin and other distinct bands above it showing pattern similar to positive control of α-fucosidosis (Fig. 4). Enzyme activity of α-fucosidase in leukocytes was 1 nmol/h/mg protein which was less than 1% from normal mean. These two laboratory methods confirmed the diagnosis.

2.2. Patient 2

Patient 2 was the younger brother of patient 1. He was 3 year old at the time of evaluation for psychomotor regression, which started at 12 months of age.

Figure 2 (a: patient 1, b: patient 2): Showing mild facial coarsening, spastic Quadraparesis and scissoring posture.

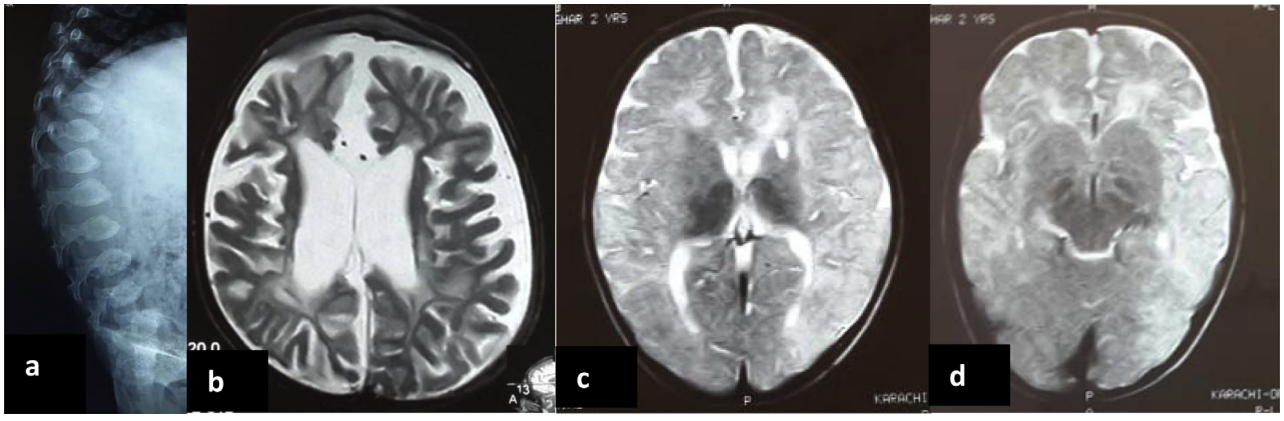

Figure 3 (a) (Patient 1) shows anterior beaking of thoraco-lumbar spines. (b) (Patient 1; MRI brain T2WI) shows a decrease in the volume of white matter. (c and d) (Patient 2; MRI brain T2WI) shows hypointense signals in bilateral thalami & substantia nigra.

He was born after an uneventful full-term pregnancy. The parents reported normal growth and development till 12 months of age. He had just started cruising when parents noted progressive spasticity of body limiting his ability to cruise and eventually he was unable to sit or hold neck and was unable to follow simple instructions. Unlike his brother, aspiration during feeds was not reported. At the time of clinical assessment his weight, height and head circumference was 11.4 kg, 87 cm and 42 cm respectively (all < 5th percentile).

Physical examination revealed scissoring posture and hepatosplenomegaly (Liver of 4 cms below right coastal margin and spleen of 3 cms in the long axis). Fig. 2b. He was also noted to have spastic quadraparesis with increased deep tendon reflexes. No corneal clouding, contractures or cutaneous changes and facial coarsening were noted. Cherry red spots were not noted on ophthalmological examination. X-ray spine showed an anterior breaking of lumbar vertebrae. The MRI brain showed hypo-intense signals in bilateral thalami and substantia nigra. Fig. 3c and d.

Urinary oligosaccharide analysis showed a similar pattern to that of his brother. Final diagnosis of α-fucosidosis was made based on undetectable enzyme activity of fucosidase in his leukocytes.

3. Discussion

Based on age of presentation and life expectancy two types of α-fucosidosis; type I and type II have been described [5]. Type I manifests around 6 months of age, is characterized by rapid psychomotor regression and death within the first decade of life. Type 2 presents with psychomotor regression between 12

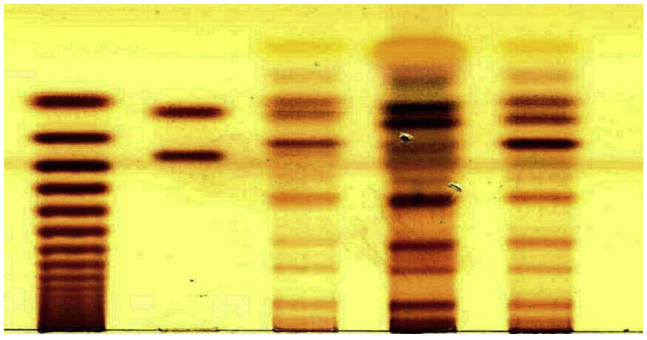

Figure 4 One-dimensional TLC plate of urinary oligosaccharides. Lane 1: dextran hydrolysates. Lane 2: standards of galactose (upper) and raffinose (lower). Lane 3: fucosidosis-positive control urine from ERNDIM. Lane 4: patient #1, Lane 5: patient #2.

and 24 months of life and has longer survival. However, a clear clinical distinction between type I and II does not exist, but they seem to be in a continuous clinical spectrum. Based on the age of presentation we can classify our patients as α-fucosidosis type II.

Both patients described here exhibited same severity and course. The intra-familial variability in clinical presentation reported previously [4,6] was not observed in this family. The MRI brain findings; decreased white matter volume along with low signals in thalami and substantia nigra on T2WI seen in our patients were comparable to the classic features described for α-fucosidosis [7].

The actual frequency of α-fucosidosis is unknown but is expected to be underestimated due to difficulty in establishing a definitive diagnosis especially in resource limited countries. Thus a clinical approach aided by simple measures like ascertainment of the presence or absence of dysostosis multiplex, coarse facies, cherry red spots and organomegaly aids in narrowing the differential diagnosis of neurodegenerative disorders to reach to the diagnosis of α-fucosidosis. Early diagnosis of α-fucosidosis may alleviate the natural course of the disease as clinical improvement has been reported in human α-fucosidosis after hematopoietic stem cell transplantation HSCT [8].

Conflict of interest

The authors declare that they have no conflict of interest.

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