

Fucosidosis in a Chinese boy: a case report and literature review

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Abstract

Fucosidosis is a rare lysosomal storage disease, resulting from a deficiency in an alpha-L-fucosidase enzyme. There are fewer than 120 cases of this disease worldwide and very few reported in Chinese children. Here, we report a Chinese boy presenting with psychomotor regression, dermatological abnormality, dysostosis multiplex, and classic changes observed with head magnetic resonance imaging. He was diagnosed with fucosidosis, with a previously reported homozygous mutation of c.393(exon2)T > A, p.Tyr131Stop, in the *FUCA1* gene. Increasing awareness of fucosidosis will help in the early diagnosis of this disease and could shed light on the therapeutic role of hematopoietic stem cell transplantation, which may be effective in early stages of the disease.

Keywords

Fucosidosis, *FUCA1*, lysosomal storage disorder, telangiectasia, psychomotor regression, alpha-L-fucosidase

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Introduction

Fucosidosis is a lysosomal storage disorder caused by mutations in the *FUCA1* gene, which encodes alpha-L-fucosidase enzyme. Alpha-L-fucosidase catalyzes the cleavage of fucosyl residues from entire glycoconjugates. With reduced or absent activity of the enzyme in fucosidosis, degradation of

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fucosylated glycoproteins and glycolipids becomes impaired in lysosomes, and more than 20 fucosylated substrates are deposited in different tissues, which leads to variable symptoms. Fewer than 120 cases have been reported worldwide.¹ Most occur in people of Italian descent and in Mexican-Indian populations of New Mexico and Colorado;² only four cases have been reported in the Chinese population.³⁻⁵ Here, we reported a fifth case, a Chinese boy diagnosed with fucosidosis.

Case report

An 8-year-old Chinese boy with a 2-year history of abnormal gait and born to non-consanguineous parents, presented to Quanzhou Children Hospital (Quanzhou, China). No family history of neurodegenerative disease was reported, and the patient had an uneventful perinatal history. His psychomotor milestones were normal during the first 8 months of life. However, he developed psychomotor regression after that time. At 1 year and 7 months, he was able to stand without support and walk alone but was prone to falling. In the two years before presenting to the hospital, he had progressive motor deterioration and walked on his toes, which made him

fall frequently. He also had language developmental delay and was able to spell only one- or two-syllable words. A pink maculopapular rash was found in the genital area at birth, which extended to the whole body, including palms and soles, with increasing age. This finding was recognized as suspected telangiectasia (Figure 1a-c). The boy had a respiratory infection every 1 or 2 months, even though immunological investigations were normal. Physical examination showed dry skin and slight facial coarseness, with a protruding forehead, arcuated eyebrows, and broad eye gap. His lips were thick and no macroglossia was observed. Muscle tension was high in the lower limbs, especially in the lower extremity, resulting in plantar flexion. Brisk bilateral deep tendon reflexes were found in the lower limbs. His intelligence quotient was <40. Lateral radiology of the cervical, thoracic, and lumbar spine showed oval vertebral bodies and anterior beak-like formations with osteoporosis (Figure 2a-c). The frontal radiology of the pelvis showed irregular femoral capital epiphyses, with possible sclerosis. The acetabular roofs were steep with an angle of approximately 30° bilaterally, and the lower iliac part was constricted (Figure 2d). Echocardiography was normal, and no visceromegaly was

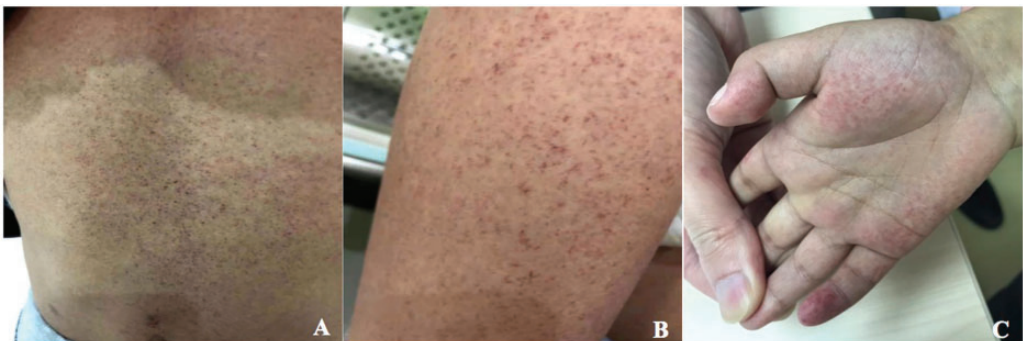


Figure 1. Maculopapular rash on the patient (a-c). Punctiform or speckled papules of a pink or dark-red color on abdomen (a), forearm (b), and palm (c) of the patient. He also had mild morphological features with dry skin, arcuated eyebrows, and broad eye gap.

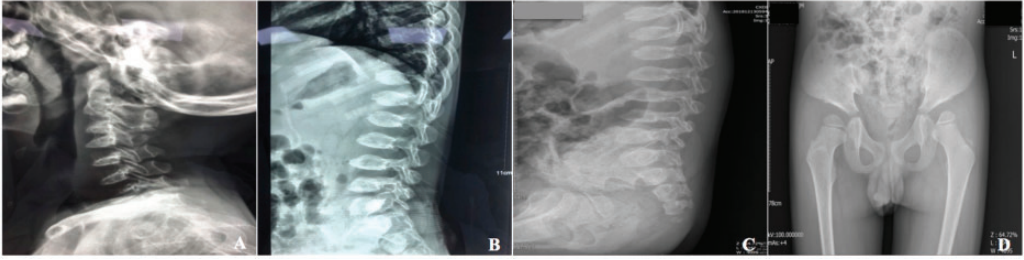


Figure 2. Radiology of spine (a–c) and pelvis (d). Lateral radiology of the cervical (a), thoracic (b), and lumbar spine (c) demonstrated anterior beak-like formation and oval-shaped vertebral bodies with osteoporosis. Frontal radiology of pelvic showed irregular femoral capital epiphyses and steep acetabular roofs with an angle of approximately 30° bilaterally (d).

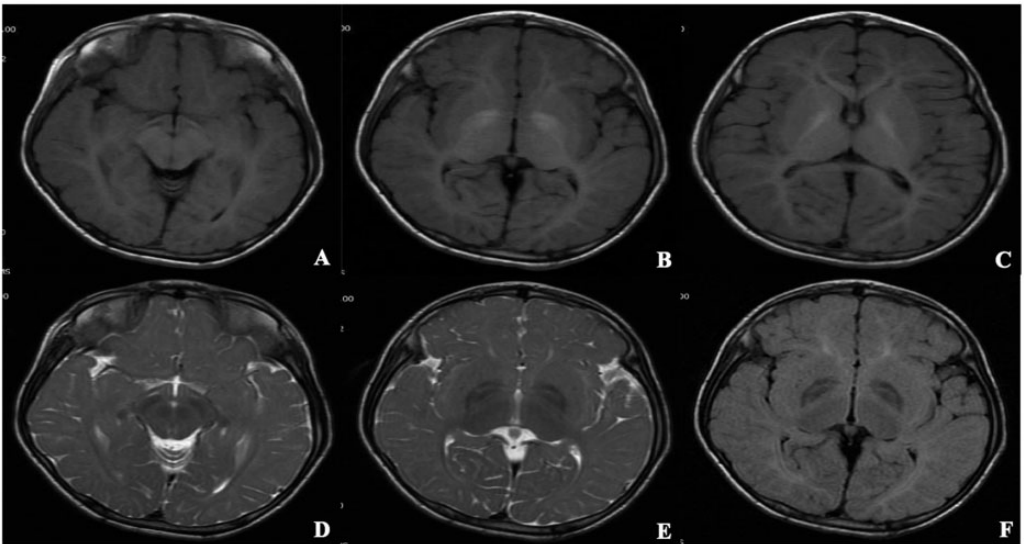


Figure 3. T1-weighted axial (a–c), T2-weighted axial (d, e), and FLAIR (f) MRI. In the bilateral pallidum, axial MRI showed high signal intensity on T1-weighted (a–c) and low signal intensity on T2-weighted and FLAIR images with curvilinear high-signal intensity within lentiform nuclei (d–f). Symmetric hyperintensity in bilateral periventricular white matter on T1- and T2-weighted images was consistent with hypomyelination (b–e). FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging.

found. Head magnetic resonance imaging (MRI) showed T1-hyperintense and T2-hypointense areas in the bilateral pallidum with curvilinear T2-hyperintense areas within lentiform nuclei, a sign sometimes called “eye of the tiger.” Hyperintense regions on T1- and T2-weighted images were observed in symmetric periventricular white matter (Figure 3); however, no atrophy

was observed. Screening for inherited metabolic diseases, including Fabry disease, mannosidosis, and mucopolysaccharidoses, was negative. Because of the MRI “eye of the tiger” finding, a mutation in the *PANK2* gene was assumed; however, analysis of this gene showed no mutation. Next-generation sequencing indicated a homozygous mutation in the *FUCA1* gene, c.393(exon2)T>A,

p.Tyr131Stop, which has been described previously. The patient was diagnosed with fucosidosis.

All identifying details of the patient's information have been deleted from the case report, and the identity of the patient cannot be ascertained in any way; therefore, signed consent from the patient or his parents was deemed unnecessary. The patient's parents consented to publication of the patient's history.

Discussion

Symptoms of fucosidosis include coarse facial features, visceromegaly, neurologic disorders, dysostosis multiplex, and angiokeratomas. However, it is important to note that symptoms vary considerably. Fucosidosis can be categorized into two types:^{2,6,7} type 1 begins in early infancy, usually at about 6 months of age, and has a more rapid progression, especially in neurologic deterioration; type 2 initiates before the age of 2 years and progresses more slowly. Individuals with type 1 often die between the age of 5 and 10 years, whereas patients with type 2 might survive to the second decade, although rarely to the age of 30.^{2,6,7} However, current opinion is that severity of the clinical disorder might exist on a continuum rather than two clear-cut distinct types as considered previously.^{2,7}

No relationship has been found between clinical severity and specific mutation or residual activity of alpha-L-fucosidase.⁷ It is difficult to accurately classify our patient as being either type 1 or type 2, but we speculate he might be type 2 because most of his symptoms appeared after 8 months and the disease did not progress rapidly. Our patient has most symptoms of fucosidosis except visceromegaly, and the clinical course echoes that of fucosidosis.

The first observed symptom in our patient was telangiectasia. Telangiectasia or angiokeratoma is a skin change observed

in fucosidosis. In a review of 77 fucosidosis patients, about 51% presented with angiokeratoma.⁷ The presence or absence of angiokeratoma likely depends on the age of the patients examined; angiokeratoma is more likely to be found in older patients. Only about 34% of patients below 10 years of age have angiokeratoma, whereas 88% of patients older than 20 years show the skin change.⁷ At the initial patient assessment, angiokeratoma might present as simple telangiectasia and later develop into angiokeratoma. However, some patients have only telangiectasia without angiokeratoma.^{7,8} In our patient, telangiectasia was found, and it is unknown whether angiokeratoma will appear as time passes. The mechanism underlying the dermatological abnormality is unclear. It is speculated that accumulation of pathologic materials, including a partial breakdown of glycolipids and glycoproteins, leads to apoptosis of endothelial cells, and then these cells continuously regenerate, which results in ecstatic capillaries.⁹ An ultrastructure study has found varying degrees of vacuolation in melanocytes, endotheliocytes, and sweat gland cells of skin.¹⁰

The MRI of our patient showed a hypointense globus pallidus with linear hyperintense inside on T2 images. The low signal on T2 in the globus pallidus has been described previously in fucosidosis,¹¹ although the underlying mechanism is unclear. Several explanations, including cerebral glycolipid and triglyceride deposition and accumulation of calcification or iron following subacute hemorrhage, have been proposed.^{11,12} The hyperintense view of the T2 images in periventricular white matter in our patient indicated demyelination, which might also affect subcortical white matter,¹¹ although it was not obvious in our case. One reported case showed increased cerebellar volume in the early stage of fucosidosis,¹³ but generalized cerebral atrophy becomes prominent with

clinical deterioration.⁶ No obvious atrophy was found in our case; however, a follow-up is necessary to monitor changes.

The genetic alteration observed in our patient has been reported previously and is known to result in a stop codon that would truncate the protein at amino acid position 131 and thus affect activity of the alpha-L-fucosidase enzyme. To date, about 30 *FUCA1* mutations have been reported in the literature;^{14–16} most are nonsense mutations consisting of point mutations and deletions or insertions, but a minority are missense mutations. Missense mutations might imply the presence of residual enzyme activity or compensatory enzyme pathways and thus modulate the severity of clinical symptoms.³ Treatment of fucosidosis is a major challenge. There is currently no approved treatment for the neurological disease-related symptoms in fucosidosis, and management of the disorder is limited to supportive therapy. Enzyme replacement treatment, including that delivered via the cerebrospinal fluid, and substrate inhibition are still in the preclinical stage,¹⁷ and their translation to humans remains speculative. Hematopoietic cell transplantation,^{5,18} such as bone marrow or umbilical cord blood transplantation, has attracted considerable attention because it could provide enzyme-producing cells that are self-refreshing and permanent and that secrete the active enzyme. This approach has been examined in preclinical models,^{18,19} but the effect of transplantation is limited to the early stage of fucosidosis, and the risks and long-term outcomes must be considered. Hematopoietic cell transplantation might be controversial in our patient with a neurologic disorder.

Conclusion

Fucosidosis is a rare disorder. Telangiectasia or angiokeratoma might be an early indicator but is inconspicuous in

the early stage of the disease. Paying attention to the classic symptoms, including visceromegaly, neurological deterioration, dysostosis multiplex, and neuroimaging, is critical for accurate diagnosis. Hematopoietic stem cell transplantation may be a suitable therapeutic approach in the early stage of the disease; thus, early diagnosis is necessary.

Authors' contributions

LW and MY were major contributors in writing the manuscript; JZ and HH analyzed and interpreted the data; and SH and TT helped to collect the patient data. All authors read and approved the final manuscript.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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