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

Lingxing Wang1,*, Meili Yang1,* Shanyan Hong1, Ting Tang1, Jiaxin Zhuang2 and Honghong Huang1

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

Date received: 17 October 2019; accepted: 12 February 2020

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

1Department of Neurology, Second Affiliated Hospital of Fujian Medical University, Quanzhou, Fujian, China
2Department of Pediatric Neurology, Quanzhou Children Hospital, Quanzhou, Fujian, China
*These authors contributed equally to this work.
Corresponding author:
Jiaxin Zhuang, Department of Pediatric Neurology, Quanzhou Children Hospital, Fengze Street 700, Quanzhou 362000, Fujian, China.
Email: zhuangjx123@126.com

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (https://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).
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. Most occur in people of Italian descent and in Mexican-Indian populations of New Mexico and Colorado; only four cases have been reported in the Chinese population. 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.
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 angio-keratomas. However, it is important to note that symptoms vary considerably. Fucosidosis can be categorized into two types: 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. 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.

No relationship has been found between clinical severity and specific mutation or residual activity of alpha-1-fucosidase. 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 angio-keratomas is a skin change observed in fucosidosis. In a review of 77 fucosidosis patients, about 51% presented with angio-keratomas. The presence or absence of angio-keratomas likely depends on the age of the patients examined; angio-keratomas is more likely to be found in older patients. Only about 34% of patients below 10 years of age have angio-keratomas, whereas 88% of patients older than 20 years show the skin change. At the initial patient assessment, angio-keratomas might present as simple telangiectasia and later develop into angio-keratomas. However, some patients have only telangiectasia without angio-keratomas. In our patient, telangiectasia was found, and it is unknown whether angio-keratomas 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. An ultrastructure study has found varying degrees of vacuolation in melanocytes, endotheliocytes, and sweat gland cells of skin.

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, 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. The hyperintense view of the T2 images in periventricular white matter in our patient indicated demyelination, which might also affect subcortical white matter, although it was not obvious in our case. One reported case showed increased cerebellar volume in the early stage of fucosidosis, but generalized cerebro-atalophy becomes prominent with
clinical deterioration.

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; 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.

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, and their translation to humans remains speculative. Hematopoietic cell transplantation, 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, 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.

**Funding**

This publication was funded by a grant from the Natural Science Foundation of Fujian (2019J01471) and Quanzhou Program of High-level Talents Innovation and Entrepreneurship (2018C050R).

**ORCID iDs**

Lingxing Wang https://orcid.org/0000-0001-5208-1795
Jiaxin Zhuang https://orcid.org/0000-0002-7917-1878

**References**

1. Gautschi M, Merlino L, Calza AM, et al. Late diagnosis of fucosidosis in a child with progressive fixed dystonia, bilateral pallidal lesions and red spots on the skin. *Eur J Paediatr Neurol* 2014; 18: 516–519. DOI: 10.1016/j.ejpn.2014.02.005.

2. Malatt C, Koning JL and Naheedy J. Skeletal and brain abnormalities in fucosidosis, a rare lysosomal storage disorder. *J Radiol Case Rep* 2015; 9: 30–38. DOI: 10.3941/jrcr.v9i5.2149.
3. Ip P, Goh W, Chan KW, et al. A novel FUCA1 mutation causing fucosidosis in a Chinese boy. *J Inherit Metab Dis* 2002; 25: 415–416.

4. Hwu WL, Chuang SC, Wang WC, et al. Fucosidosis in a Chinese girl. *J Inherit Metab Dis* 1994; 17: 255.

5. Jiang M, Liu S, Jiang H, et al. Brain abnormalities in fucosidosis: transplantation or supportive therapy? *Metab Brain Dis* 2017; 32: 317–320. DOI: 10.1007/s11011-017-9968-5.

6. Provenzale JM, Barboriak DP and Sims K. Neuroradiologic findings in fucosidosis, a rare lysosomal storage disease. *AJNR Am J Neuroradiol* 1995; 16: 809–813.

7. Willems PJ, Gatti R, Darby JK, et al. Fucosidosis revisited: a review of 77 patients. *Am J Med Genet* 1991; 38: 111–131. DOI: 10.1002/ajmg.1320380125.

8. Ben Turkia H, Tebib N, Azzouz H, et al. Phenotypic spectrum of fucosidosis in Tunisia. *J Inherit Metab Dis* 2008; 31: S313–S316. DOI: 10.1007/s10545-008-0891-0.

9. Kanitakis J, Allombert C, Doebelin B, et al. Fucosidosis with angiokeratoma. Immunohistochemical & electronmicroscopic study of a new case and literature review. *J Cutan Pathol* 2005; 32: 506–511. DOI: 10.1111/j.0303-6987.2005.00366.x.

10. Breier F, Hobisch G, Fang-Kircher S, et al. Histology and electron microscopy of fucosidosis of the skin. Subtle clues to diagnosis by electron microscopy. *Am J Dermatopathol* 1995; 17: 379–383.

11. Ediz SS, Aralasmak A, Yilmaz TF, et al. MRI and MRDS findings in fucosidosis; a rare lysosomal storage disease. *Brain Dev* 2016; 38: 435–438. DOI: 10.1016/j.braindev.2015.09.013.

12. Oner AY, Cansu A, Akpek S, et al. Fucosidosis: MRI and MRS findings. *Pediatr Radiol* 2007; 37: 1050–1052. DOI: 10.1007/s00247-007-0572-4.

13. Kau T, Karlo C, Gungor T, et al. Increased cerebellar volume in the early stage of fucosidosis: a case control study. *Neuroradiology* 2011; 53: 509–516. DOI: 10.1007/s00234-011-0855-1.

14. Inui K, Akagi M, Nishigaki T, et al. A case of chronic infantile type of fucosidosis: clinical and magnetic resonance image findings. *Brain Dev* 2000; 22: 47–49.

15. Fleming CJ, Sinclair DU, White EJ, et al. A fucosidosis patient with relative longevity and a missense mutation in exon 7 of the alpha-fucosidase gene. *J Inherit Metab Dis* 1998; 21: 688–689.

16. Willems PJ, Seo HC, Coucke P, et al. Spectrum of mutations in fucosidosis. *Eur J Hum Genet* 1999; 7: 60–67. DOI: 10.1038/sj.ejhg.5200272.

17. Kondagari GS, King BM, Thomson PC, et al. Treatment of canine fucosidosis by intracisternal enzyme infusion. *Exp Neurol* 2011; 230: 218–226. DOI: 10.1016/j.expneurol.2011.04.019.

18. Miano M, Lanino E, Gatti R, et al. Four year follow-up of a case of fucosidosis treated with unrelated donor bone marrow transplantation. *Bone Marrow Transplant* 2001; 27: 747–751. DOI: 10.1038/sj.bmt.1702994.

19. Taylor RM, Farrow BR and Stewart GJ. Amelioration of clinical disease following bone marrow transplantation in fucosidase-deficient dogs. *Am J Med Genet* 1992; 42: 628–632. DOI: 10.1002/ajmg.1320420439.