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Case Report

# Fucosidosis: clinical and molecular findings of Turkish patients

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## ABSTRACT

**Background.** Fucosidosis is a rare, autosomal recessive lysosomal storage disease caused by alpha L- fucosidase enzyme deficiency in all tissues. Here, we identify a patient with a novel homozygous pathogenic variant and atypical clinical findings and summarized the clinical and molecular features of Turkish patients reported in the literature and present.

**Case.** The patient was born to consangineous parents at the 28th week of gestation. He had developmental delay that was attributed to prematurity. At he age of 2.5 years, brain magnetic resonans imaging revealed hyperintensities of symmetrical periventricular, subcortical, centrum semiovale and corona radiata regions on T2 and FLAIR weighted images. He developed seizures and showed developmental regression at he age of 3,5 years. Beside, coarse facial features and hepatomegaly were detected on phsyical examination. Lysosomal enzyme analysis revelaed alfa fucosidase deficiency and molecular genetic analysis identified a novel homozygous pathogenic p. Lys431 fs variant in FUCA1 gene.

**Conclusions.** In Turkish patients no distinguishable clinical and radiologic finding could be established. Molecular analysis was performed in few patients. Increasing of molecular and biochemical facilities might enable to make diagnosis and increase the prevalence of the disease in countries with high rate of consanguineous marriages. Moreover, it will provide genetic counseling, and enlighten the therapeutic effects of hematopoietic stem cell transplantation.

**Key words:** fucosidosis, *FUCA1*, developmental regression, coarse face.

Fucosidosis is a very rare autosomal-recessive lysosomal storage disease. Deficiency of $\alpha$-L-fucosidase due to biallelic pathogenic variants in FUCA1 gene leads to the accumulation of glycoproteins, glycolipids, oligosaccharides, and mucopolysaccharides in various tissues including both the central and peripheral nervous system.[1]

Clinical manifestation are typically characterized by delayed motor and cognitive functions followed by progressive neurological deteriorations, associated with systemic features of a coarse face, dysostosis multiplex, recurrent respiratory infections, angiokeratoma corporis diffusum, organomegaly, ocular abnormalities, hearing loss, growth retardation, contractures, spasticity, seizures and consequently early death.[2-4]

The diagnosis is confirmed by demonstration of reduced enzyme activity and, preferably, mutation analysis.[5,6] Hematopoietic stem cell transplantation (HSCT) may reduce the severity and slow the progression of the neurological features.[7]

Here we present a patient with a novel pathogenic mutation and atypical clinical findings and identify an overview of Turkish patients in the literature.

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**Case Report**

Our patient was born as a first child to consanguineous parents at the 28th gestation week with the weight of 1150 gr by cesarean delivery. He was admitted to the neonatal intensive care unit and developed grade I-II intracranial bleeding. During his follow up, developmental milestones were delayed. Holding his head in a prone position was possible at the age of 8 months and he developed sitting without support and speech at 12 months. He had recurrent respiratory infections and his sweat chloride test was performed and found abnormal. However cystic fibrosis (CF) molecular analysis was normal. He underwent an inguinal hernia operation at 1,5-year-old and he was consulted to the Department of Orthopedics for kyphosis. At the age of 2,5 years, brain magnetic resonance imaging (MRI) showed hyperintensities of symmetrical periventricular, subcortical, centrum semiovale and corona radiata regions on T2 and FLAIR weighted images (Fig. 1). Then he developed seizures and after one week he showed rapid developmental regression as losing his sitting and speech abilities. Whole exome sequencing (WES) analysis was planned, and he was referred to our clinic at the age of 3,5 years. On physical examination, his anthropometrics were as follows: height: 92cm (3p), weight: 13.5 kg (12p) head circumference: 50 cm (35p). He had a coarse face with broad nasal bridge, hypertelorism, wide ala nasis, and minimal hepatomegaly. He was not able to cooperate and had a lack of eye contact and no response to social interaction. He had axial hypotonicity, he was not able to sit without support, he had poor head control on traction and spasticity in all four extremities. He also had dysostosis multiplex, kyphosis and pectus carinatum (Fig. 2). Physical examination and clinical findings indicate an oligosaccharidosis and his WES analysis revealed a novel pathogenic homozygous c. 1290_1299delGAAGTGGTCC (p. Lys431 fs) variant in FUCA1 gene that may result in a frameshift mutation. Leukocyte enzyme analysis showed almost a non-detectable enzyme levels which confirmed the diagnosis. Transthoracic echocardiography and fundoscopic evaluation were normal, however audiological assessment identified bilateral hearing loss.

Written informed consent was obtained from the parents of the child.

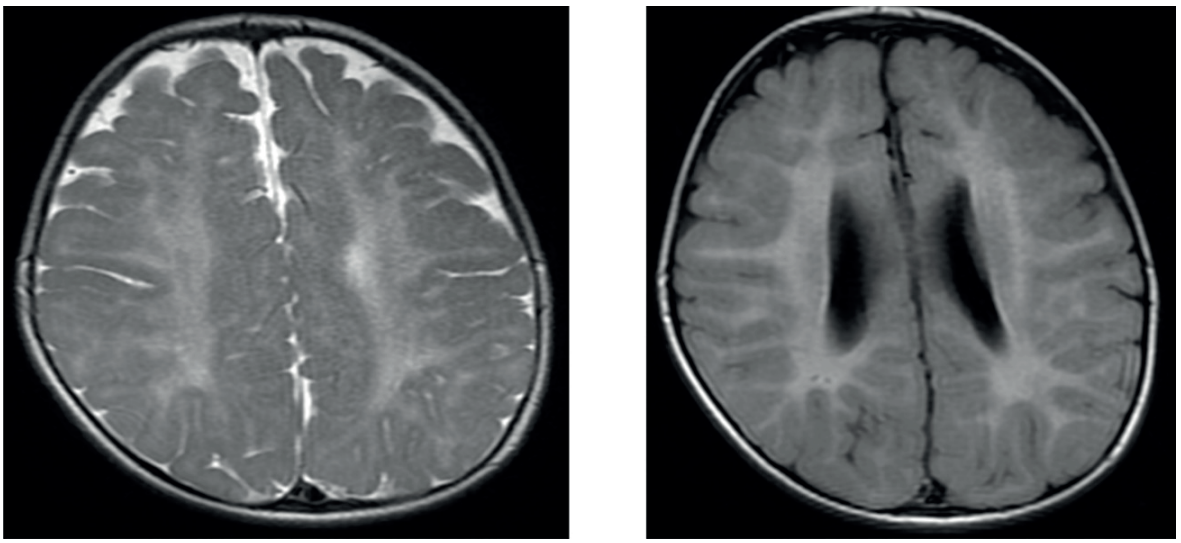

**Fig. 1.** Magnetic resonance imaging (MRI) T2-weighted axial images showing almost symmetrical hperintensities involving the peritrigonal, periventricular, subcortical, centrum semiovale, corana radiata regions.

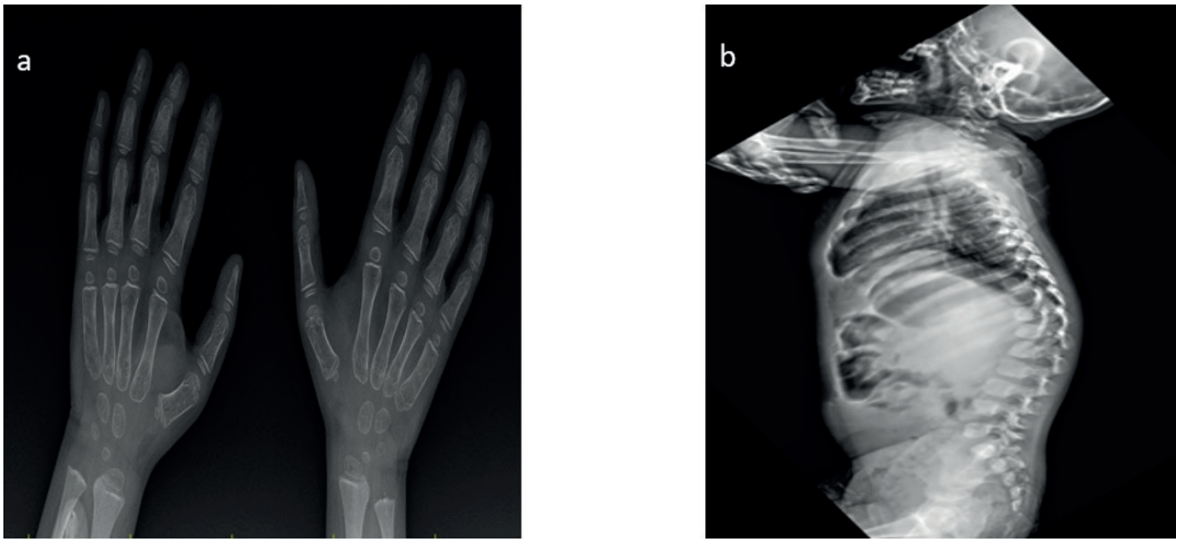


**Fig. 2.** Dysostosis multiplex of hands and vertebra. **a.** indicates irregularities of proximal metacarpals and bullet shaped distal phalanges; **b.** indicates anterior beaking of the vertebral body and gibbus deformity.

## Discussion

Alpha L-fucosidase enzyme is a homotetramer composed of subunits of different masses (50 to 60 kDa), which causes variations in N-glycosylation and proteolytic processing. 19,20 As a result of the hydrolytic enzyme deficiency, incomplete catabolism of N- and O-glycosylproteins leads to the accumulation of fucose-containing glycolipids and glycoproteins in various tissues and urine. Fucose (C6H12O6), is found in most of the plasma glycoproteins in the mucopolysaccharides and mucolipids of various human and animal tissues.[8]

Fucosidosis is a very rare disease with a very low incidence of <1/200000. 12 To date, around 120 patients were identified.[9-11] The highest incidence has been described in Italy, Mexico, Colorado and Cuba.[9,12] We could obtain clinical and molecular manifestations of 14 Turkish patients after a detailed literature investigation. The mean age of the patients was 6 years and male/female ratio was 9/5. Consanguinity was present in 11/12 families. 9 (81%) patients had developmental delay. All patients had coarse facial features, intellectual delay, developmental delay and developmental regression. Apart from one patient, all patients (90%) had growth retardation. Recurrent respiratory infections were present in 63% of the patients. Angiokeratoma corporis diffisum and dysostosis multiplex were seen in 54% of the patients. Seizure and organomegaly were accompanied in 27% of the patients. Our patient was the only patient with hearing loss involvement. Brain MRI findings of 12 patients demonstrated periventricular and, subcortical white matter abnormalities in 7 and 4 patients, cortical and midbrain involvement in 1 and 2 patients respectively. Hypointensities on T2 and hyperintensities on T1- weighted images of globus pallidus was detected in 4 patients and hypointense areas were shown in 3 patients. Cerebellar volume increasing was demonstrated in 3 patients in early stage of the disease. (Alpha L- fucosidase enzyme analysis was performed in 9 patients and low levels were detected in a total of the patients. Only 3 patients underwent molecular analysis of the FUCA1 gene and pathogenic mutations were determined in all of the patients.[13-20]

Willems et al.[2] and Wali et al.[7] reported clinical and molecular findings of 77 and 89 patients respectively. Comparison of clinical features of those patients with Turkish patients is shown in Table I. Our findings were more consistent with Willems et al.[2] report. Almost all of the percentages of clinical manifestations in the

**Table I.** Comparision of prevelance of clinical findings in the literature.

| | Wiliam et al.[2] | Wali et al.[7] | Turkish Cases |
|---|---|---|---|
| Mental retardation | 73 (95%) | 50-60% | 14 (100%) |
| Neurologic regression | 68 (88%) | 50-60% | 14 (100%) |
| Coarse face | 61 (79%) | 70-80% | 11 (100%) |
| Growth retardation | 60(78%) | 30-40% | 10 (90%) |
| Recurrent infections | 60 (78%) | 30-40% | 7 (63%) |
| Dysostosis multiplex | 45 (58%) | 50-60% | 6 (54%) |
| Angiokeratoma | 40 (52%) | 40-50% | 6 (54%) |
| Seizure | 29 (38%) | 10-20% | 3 (27%) |
| Organomegaly | 23 (30%) | 30-40% | 3 (27%) |
| Hearing loss | 9 (12%) | 10-20% | 3 (27%) |
| Hernia | 7 (9%) | - | 1 (9%) |
| Ophthalmologic findings | 5 (6%) | <10% | - |

study by Wali et al.[7] were lower than the Willems et al.[2] 's and ours. Particularly growth retardation was present in 30-40% of the patients in the report by Wali et al.[7], however, in Willems et al.[2] and in our report the percentages were 78% and 90% respectively. Growth retardation becomes more prominent with age and severity of the disease. The difference in the growth retardation rates in different studies might be associated with the difference in age and disease severity. The most common finding was intellectual disability in Willems et al.[2] and our report, however it was coarse face in Wali et al.[7] Hearing loss, hernia and ophthalmologic findings are the least frequent findings in all reports. Amongst the Turkish patients our patient was the only patient with hearing loss. In addition, hypothyroidism in Case 2, and angiokeratoma only on the tongue and gingiva in case 12 were the remarkable distinct findings.

In our patient, a striking finding was the positive sweat chloride test. Several authors have noted possible links between fucosidosis and CF. Both disorders are associated with high sweat electrolytes and recurrent infections of the respiratory tract without a recognized defect in systemic immunity.[21] Fucosidosis patients often have recurrent infections confined to areas of mucus-secreting ciliated epithelia. It was proposed that the terminal sugars fucose and sialic acid play a major role in defining the viscoelasticity of mucus. Therefore, alterations in the enzymatic cleavage of these sugars affect mucus cross-linking and its viscoelasticity. Without cross-linking, cilia would flail about ineffectively in watery secretions.[8]

Classical MRI findings include bilateral globi pallidi hyperintensities on T1- and marked hypointensity on T2-weighted images. In addition, there may be diffuse symmetric white matter hyperintensities on T2-weighted images with normal appearance on T1-weighted images, indicative of hypomyelination.[7] In Turkish patients all of the MRIs were abnormal, and the manifestations were heterogenous (Table II). In case 12 there were hyperintense signal alterations on T1-weighted imaging and hypointense signal alterations on T2-weighted imaging in bilateral globus pallidus, substantia nigra, and nucleus ruber. Corpus callosum thinning and superior vermian atrophy was observed. This finding caused misdiagnosis of the elder brother as neurodegeneration with brain iron accumulation disorders (NBIA) which is one of the diseases that can present itself with the same bilateral pallidal hypointensity image on T2; whereas, it does not cause hypomyelinization and atrophy like fucosidosis.[19] In case 2 in addition to cortical atrophy, focal nodular signal abnormalities in the brainstem on T2- weighted images were shown. Interestingly, in 3 siblings reported by

**Table II.** Clinical, molecular and radiologic features of Turkish patients.

| References | Case No | Sex | Age of Onset (y) | Consang. | Developmental history | Enzyme analysis/Mutations | Cranial Imaging |
|---|---|---|---|---|---|---|---|
| Seo et al.[13] | 1 | M | 1 | + | Diagnosed with fucosidosis at the age of 1 due to progressive neurological regression, spasticity, contractures, coarse facies, hepatosplenomegaly, growth retardation, and angiokeratoma corporis diffusum. He did not develop any speech skills and was bedridden until his death at the age of 22 | Negligible enzyme activity in cultured skin fibroblasts/ c.773delA, p.(Glu258Glyfs*3) | NA |
| Mungan et al.[14] | 2 | M | 1,5 | + | He smiled to his mother at three months, sat with support at 12 months, and walked at 18 months. Afterwards his developmental delay became more obvious. He developmentally regressed, losing his ability to walk. He never uttered any meaningful words. His past medical history was also remarkable for recurrent pulmonary infections and myoclonic seizures | No enzyme activity in leukocytes/NA | Cortical atrophy, and focal nodular signal abnormalities in the brainstem on T2- weighted images |
| Kanitaksis et al.[15] | 3 | F | 9 | + | She presented severe growth and mental retardation and angiokeratomas predominating over the lower trunk, the abdominal wall, the buttocks, external genitalia, and upper thighs. Smaller, lesions were also found on the gingiva and the lips | Almost complete absence of leokocyte enzyme lactivity/ NA | NA |
| Öner et al.[16] | 4 | F | 6 | + | She demonstrated moderate growth and mental retardation until 3 years of age, never developing expressive language or walking without support. She then showed rapid developmental regression and psychomotor deterioration, subsequently becoming severely spastic with dystonic movements of her right arm and jaw and losing all psychosocial responses | Almost complete absence of leukocyte enzyme activity/ NA | Symmetrical hyperintensity in the periventricular and subcortical white matter on T2-weighted images, hyperintensity on T1- and hypointensity on T2-weighted imaging in bilateral globus pallidus, |

Consang: consanguinity, y: year, m:month, a and b indicate siblings, NA: Non available

**Table II.** Continued.

| References | Case No | Sex | Age of Onset (y) | Consang. | Developmental history | Enzyme analysis/Mutations | Cranial Imaging |
|---|---|---|---|---|---|---|---|
| Kılıç et al.[17] | 5[a] | F | 8 | + | Mental Motor retardation, subsequently psychomotor deterioration | Low enzyme activity in cultured fibroblast cells/NA | Atrophy of pervebtricular white matter and hypointensities in thalamus |
| | 6[a] | F | 16 | + | Mental Motor retardation, subsequently psychomotor deterioration | Low enzyme activity in cultured fibroblast cells/NA | Atrophy of pervebtricular white matter and hypointensities in thalamus |
| | 7[a] | M | 12 | + | Mental Motor retardation, subsequently psychomotor deterioration | Low enzyme activity in cultured fibroblast cells/NA | Atrophy of pervebtricular white matter and hypointensities in thalamus |
| Kau et al.[1] | 8[b] | M | 25 m | + | Developmental delay and regression | Low enzyme activity an mutation analysis | İncreased cerebellar volume |
| | 9[b] | M | 20 m | + | Developmental delay and regression milder than the twin brother case 8 and underwent bone marrow transplantation | | İncreased cerebellar volume |
| | 10[b] | M | 2m | + | Daignosed at 2 months of age and underwent bone marrow transplantation at 4 months of age | | |
| Kılıç E et al.[18] | 11 | M | 12 | + | His early developmental milestones were normal until two years of age . He then began to deteriorate in all developmental fields. At age 12, he had deteriorated significantly. There was intellectual delay with no speech, an inability to walk without support and an evident pattern of behavioral irritability. | Low leukocyte enzyme activity/NA | Symmetric periventricular white-matter hyperintensities contrasting with low intensities on the basal ganglia on T2 weighted images |

Consang: consanguinity, y: year, m:month, a and b indicate siblings, NA: Non available

**Table II.** Continued.

| References | Case No | Sex | Age of Onset (y) | Consang. | Developmental history | Enzyme analysis/Mutations | Cranial Imaging |
|---|---|---|---|---|---|---|---|
| Zübarioğlu et al.[19] | 12 | F | 7 | - | She developed normal until 12 months of age. She began unsupported walk at 15 months and became gradually unsteady and was lost soon after 5 years of age. She had a complete loss of voluntary movements including head control. Choreathetoid movements, especially marked on arms. There were red streaks on gingivae and blue-brown spots on tongue | Low enzyme activity in plasma, leukocytes, and cultured fibroblasts | Mild hyperintensity in cerebral deep white matter and subcortical areas bilaterally, hyperintensity on T1- and hypointensity on T2-weighted imaging in bilateral globus pallidus, substantianigra, and nucleus ruber. Corpus callosum thinning and superior vermian atrophy was also observed |
| Ediz et al.[20] | 13 | M | 4 | + | He started to seat with unassisted after one year and to walk at age of 27 months. He could not speak any meaningful words. He was referred with recurrent upper respiratory tract infections in four months and treated like an asthma patient. There was hypertonicity in lower extremities | NA/ c.244C > T, p.Gln82* Nonsense mutation, truncated protein | Combination of hypointensity in the medial and lateral pallidal segments of the globus pallidus and hyperintensity in its laminae on T2-W. |
| Our patient | 14 | M | 3,5 | + | Developmental delay, seizure and neurologic regression at 2,5 years of age | Almost complete absence of leukocyte enzyme activity/ c. 1290_1299delGAAGTGGTCC (p. Lys431 fs) | Symmetric white-matter hyperintensities on T2 weighted images on periventricular and subcortical, centrum semiovale, corona radiata regions |

Consang: consanguinity, y: year, m:month, a and b indicate siblings, NA: Non available

Kau et al.[1], increased cerebellar volume was detected in early childhood which was a novel finding.

The diagnosis of fucosidosis is made by measuring the enzyme activity or by molecular analysis of FUCA1 gene. To date, 41 pathological variants of FUCA1 gene encoding alpha L-fucosidase has been identified (www.hgmd.cf.ac.uk; updated 03 October 2021).[22]

All mutations result in an almost total absence of enzyme activity suggesting that clinical heterogeneity is associated with not only residual enzyme activity but also with unknown factors.[22]

In Turkish patients, only 3 molecular analysis was reported and our patient is one of them. We report a novel homozygous deletion leads to a frameshift mutation. The other mutations were nonsense and frameshift mutations.

The management of fucosidosis is challenging. There is still no approved therapy for neurologic findings of the disease and the main management strategy is supportive with physiotherapy and other allied health input. The multidisciplinary team usually involves metabolic physicians, physiotherapists, ophthalmolog, orthopedic, cardiology and neurology specialists. Enzyme replacement therapy via cerebrospinal fluid and substrate inhibition therapies are under preclinical stages. HSCT via umbilical cord blood and bone marrow transplantation are the treatment options. HSCT was applied in a small number of patients with fucosidosis with symptoms stabilization in some early diagnosed cases however the long-term results are controversial.[8] In addition, individuals are often considered unsuitable for transplantation because they are diagnosed with advanced disease. HSCT was applied to 2 of the Turkish patients. They were siblings and case 9 had mild disease, and case 10 underwent HSCT at the age of four months before the development of clinical manifestations. However, there was no data regarding their neurologic progress. HSCT in our patient is controversial as he has neurologic manifestations.

We report a fucosidosis patient with seizure onset developmental regression. In lysosomal storage diseases seizure is generally a feature of late stages of the disease. The patient is also distinguished from the other patients by having hearing loss and a hernia. In addition, in our patient despite symmetrical periventricular white matter abnormalities, there was no globus pallidus involvement.

In Turkish patients, there were no clinical and radiologic findings to distinguish them from those in the literature. Patients had common clinical features such as coarse face, developmental delay, neurologic regression, and non-common features such as angiokeratoma, seizure and hearing loss. On the other hand, radiologic features also showed heterogeneity among the patients; some patients only had hypomyelination while some also had basal ganglia and brain stem involvement..

**Ethical approval**

Written informed consent was obtained from the parents of the child.

**Author contribution**

The authors confirm contribution to the paper as follows: study conception and design: MEŞ, SU; data collection: MEŞ, SU; analysis and interpretation of results: MEŞ; draft manuscript preparation: MEŞ. All authors reviewed the results and approved the final version of the manuscript.

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**Conflict of interest**

The authors declare that there is no conflict of interest.

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