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Letter to the Editor (Case report)

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Fucosidosis mimicking juvenile idiopathic arthritis

Key message

- Fucosidosis is an exceptionally rare lysosomal storage disease, which can mimic JIA.

SIR, We present a 15.5-year-old female with fucosidosis mimicking polyarticular JIA. The patient was a female child, the second child born to non-consanguineous parents, with no adverse perinatal events. Three siblings were well. Global developmental delay of unknown aetiology was documented at 3 years old.

Aged 4 years, she developed swollen, painful knees, hips, wrists, hands and feet. There was absence of coarse facies. ANA was positive (1:1280), but other autoantibodies were negative. ESR was 80 mm/h (normal <10); CRP was consistently normal. Urine screening for mucopolysaccharidoses revealed normal urinary GAG, urine screening for oligosaccharides was normal, and abdominal US scan did not reveal hepatosplenomegaly. She was therefore diagnosed with polyarticular JIA, on the background of global developmental delay.

She initially responded well to CSs and MTX; however, at the age of 10 years, her joint disease became much more progressive, particularly of the hips, with bilateral synovial thickening of both hips with active synovitis suggested by contrast-enhanced MRI, and flattened, irregular oedematous femoral epiphyses, consistent with severe active erosive JIA. She subsequently cycled through multiple DMARDs and courses of CSs: prednisolone (maximum 40 mg/day), MTX (10–17.5 mg/week), s.c. etanercept (25 mg/week), i.v. tocilizumab (8 mg/kg 4 weekly). She has also received multiple joint injections. Of all these treatments, the patient reported maximal relief from i.v. tocilizumab. Despite that, her arthropathy progressed relentlessly (Fig. 1A), requiring right radial epiphysiodesis for progressive ulnar deviation of the right wrist (aged 12 years; Fig. 1B) and bilateral hip joint replacements aged 15 years. In view of that, and the development of more coarse facies over time (Fig. 1C), and growth failure (height <0.4th percentile) not explained by CS toxicity or systemic inflammation, her diagnosis was re-evaluated.

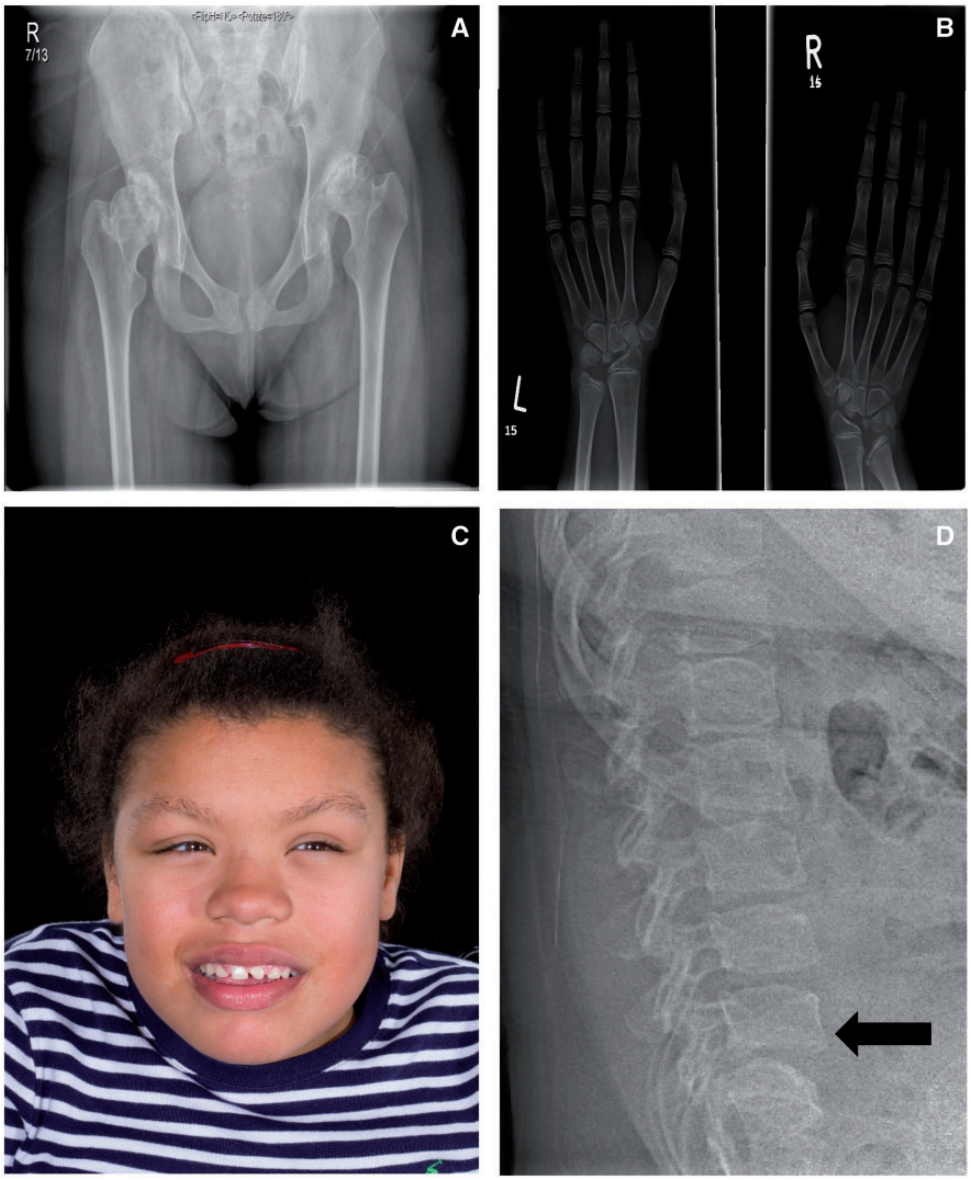
Brain MRI revealed global underdevelopment of the brain, with hypomyelination, cerebellar hypoplasia and excessive mineralization of the globi pallidi, consistent with a lysosomal storage disease (LSD). X-rays revealed small thoracolumbar vertebrae with anterior tonguing (Fig. 1D), short odontoid peg, cervical platyspondyly and broad ribs, compatible with an LSD. Biochemical screening revealed low α-fucosidase in white blood cells (0.4 nmol/h/mg; normal 25–156 nmol/h/mg) and low plasma α-fucosidase (17 nmol/h/mg; normal 175–1403 nmol/h/mg). Next-generation sequencing of *FUCA1* revealed compound heterozygous mutations: c.750C>A, p.Tyr*, leading to premature truncation of the FUCA1 protein; and c.1399_*15del, p.(*467Lysext*73), which disrupts the *FUCA1* termination codon and extends the protein by 73 amino acids. This genotype was therefore confirmatory of fucosidosis.

Fucosidosis is a rare autosomal recessive LSD caused by bi-allelic mutations in *FUCA1* [1], resulting in deficiency of the α-L-fucosidase enzyme and the secretion of fucosyl-oligosaccharides [2]. The defective enzyme cannot lyse fucose-containing glycol-conjugates, leading to the intracellular accumulation of fucose in tissues [3]. Clinical features include progressive psychomotor retardation, coarse facies, growth retardation, recurrent infections, dysostosis multiplex, angiokeratoma, visceromegaly and seizures [4]. Fucosidosis has been classified into types I and II, depending on the severity of the clinical phenotype, but the disorder is now more commonly considered as a continuous clinical spectrum with variable severity of phenotype [4].

Absence of key clinical hallmarks of fucosidosis, such as angiokeratoma and visceromegaly, early absence of coarse facies, predominance of features compatible with JIA (joint swelling, synovitis and ANA positivity) and a negative urinary oligosaccharide screen contributed to diagnostic delay in our patient. To the best of our knowledge, this is the first case report of fucosidosis presenting as JIA. Although it is possible that there was dual pathology (i.e. polyarticular JIA and fucosidosis), it is more likely that the whole phenotype is entirely explained by fucosidosis, with a secondary anti-inflammatory effect of tocilizumab for destructive joint disease in that context.

It has been suggested that clinical screening by clinical examination looking for the presence of joint contractures, combined with urinary GAG analysis and other routine laboratory measures such as ESR and ANA, might differentiate mucopolysaccharidoses from JIA [5]. This approach would have failed to distinguish JIA from fucosidosis in this case, because the patient did not have joint contractures, did have elevated ESR and positive ANA, and had negative urine screening for GAG. Therefore, clinicians must remain ever vigilant to the possibility of LSD mimicking JIA, particularly if clinical trajectories are unexpectedly poor despite DMARDs

Fig. 1 skeletal and facial abnormalities consistent with a diagnosis of fucosidosis



(**A**) Pelvic X-ray, showing grossly abnormal hip joints, with superior subluxation of femoral heads and bilateral geode formation. Both femoral necks are shortened. (**B**) X-rays of both hands and wrists (before her right epiphysiodesis), showing bilateral ulnar shortening, with deficiency of the medial radial epiphyses at both wrists. Proximal carpal row is grossly deficient bilaterally, but worse on the right. (**C**) Facial coarsening at 15 years of age. (**D**) Spinal X-ray, showing small thoracolumbar vertebrae with anterior tonguing (arrowed).

and biologics. Furthermore, a negative urinary oligosaccharide screen, attributed in this case to the clinical phenotype being at the attenuated end of the spectrum, does not exclude a diagnosis of LSD. Therefore, we add fucosidosis as an important but rare differential diagnosis for JIA, emphasizing that urinary screening of GAG does not detect this rare LSD, which requires specific lysosomal storage enzyme analysis in plasma and leucocytes, followed by genetic screening for *FUCA1* mutations. Unfortunately, there is no specific treatment for fucosidosis.

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