Short stature, dysostosis multiplex and storage disorder: mucolipidosis II

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DESCRIPTION

A girl in early childhood presented with global development delay, short stature and coarse facial features. She was born to non-consanguineous parents with no complications detected antenatally and had a normal birth weight. She had postnatal growth arrest in the second year of life. Family history was unremarkable. There was no history of recurrent infections, breathing, feeding difficulties, seizures or excessive startle response. On examination, she had coarse facial features, prominent nares, hypertrophied gingivae, proptotic eyes, prominent metopic suture, low set ears, golden hair, short neck, hoarse voice, hepatomegaly, normal cornea and bilateral fundi, and skeletal deformities including pectus carinatum, kyphoscoliosis, limited hip extension, genu valgum and flat feet. She was severely stunted (height 68.5 cm, −6.3 Z-score) and underweight (weight 9.2 kg, −2.7 Z-score). Her head circumference was 45 cm (−2 Z-score) and upper:lower body segment ratio was 1.49 (normal 1.3). A clinical diagnosis of lysosomal storage disorders was considered. Investigations showed dysostosis complex (figure 1A–C).

Complete haemogram, liver, kidney and thyroid function tests, and vitamin D levels were normal. 2D-echocardiography and ultrasonogram of abdomen were normal. MRI of brain revealed delayed myelination. Clinical exome analysis revealed compound heterozygous variants in the *GNPTAB* gene: a heterozygous two base pair deletion in exon 19 (chr12:g.102147248_10214724 9delGA) resulting in a frameshift and premature truncation of the protein five amino acids downstream to codon 1168 (p.Leu1168GlnfsTer5), and another heterozygous three base pair deletion in exon 13 (chr12:g.102159024_102159026delAAT) resulting in the in-frame deletion of amino acids (p.Ile557del; ENST00000299314.7). The *in silico* prediction of the variants was damaging by MutationTaster2 and classified as pathogenic in ClinVar database. Multidisciplinary care was initiated for the child, including neurological assessments, endocrine evaluation, genetic consultation, physical and occupational therapy. The family is coping well.

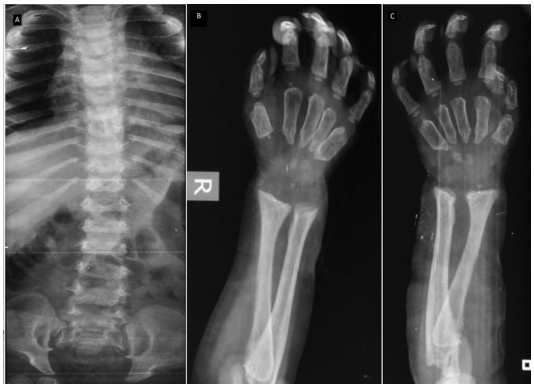

Figure 1 Clinical and radiological manifestations of MLII in a child. (A) X-ray (AP view) of the dorso-lumbar spine showing small vertebrae with reduced height and oar-shaped ribs. (B–C) X-rays of the hands showing short, wide tubular bones and pointed metacarpals with small carpals.

Mucolipidosis II (MLII; MIM#252500) is a rare, autosomal-recessive, inherited disorder associated with pathogenic variations in the *GNPTAB* gene (MIM*607840) in chromosome 12q23.2.[1] The *GNPTAB* gene codes α and β subunits of GlcNAc-1-phosphotransferase (N-acetylglucosamine-1-phosphate transferase) enzyme, which functions to prepare the lysosomal hydrolases for transportation into the lysosomes. Hence, reduced/absent GlcNAc-1-phosphotransferase levels lead to increase in several lysosomal enzymes and subsequent intracellular deficiency of these lysosomal hydrolases, resulting in building up of unaltered storage material.[1] Non-sense mutations, as well as those causing frameshift and splicing, lead to complete inactivity of GlcNAc-1-phosphotransferase resulting in MLII (also known as I-cell disease).[2] Missense mutations, on the other hand, preserve some activity of GlcNAc phosphotransferase, producing a less severe form of disease called mucolipidosis III (MLIII alpha/beta).[2] MLII presents early in infancy with development delay, coarse facial features, multiple skeletal abnormalities, decreased bone mineral density, joint contractures, gum hypertrophy, short stature and pulmonary complications.[3] Death occurs within the first decade of life due to cardiopulmonary complications.[1]

MLII shares phenotypic and radiological resemblance to mucopolysaccharidoses, but the abnormalities are first seen in the neonatal period itself in MLII, while those in mucopolysaccharidoses become evident after several months.[3] MLIII alpha/beta is milder form of disease with onset in early childhood and presents as slow growth velocity, joint stiffness, coarse facial features and less severe form of dysostosis multiplex.[3] Diagnosis of mucolipidosis is established by specific metabolic and genetic tests in patients with characteristic clinical and radiological features. Plasma enzyme assay may show increased levels of multiple lysosomal hydrolases in

plasma in both MLII and MLIII.[1] Urinary excretion of oligosaccharide is excessive but there is no glycosaminoglycanuria, thus providing a clue for differentiating mucolipidosis from mucopolysaccharidoses. The assay for GlcNAc-1-phosphotransferase activity is not routinely available, hence molecular analysis enables confirmation of diagnosis and distinguishes MLII from MLIII. More than a hundred *GNPTAB* mutations are currently known, the the most common being c_3503_3504delTC located in exon 19,[1] as was seen in our patient. MLII is a fatal disease and no specific therapy is available until now. Management involves early identification with the utility of gene sequencing and provision of supportive care to improve the quality of life.

Learning points

- We describe a severely stunted girl in early childhood with MLII presenting with coarse facies, development delay and dysostosis multiplex.
- Presence of classic clinical characteristics requires high index of clinical suspicion for differentiating from other storage disorders.
- We emphasise on the role of molecular analysis for confirmation of diagnosis and prenatal genetic testing for families with previously affected children.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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