Delayed Presentation of Rickets in a Child with Labyrinthine Aplasia, Microtia and Microdontia (LAMM) Syndrome

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Background: Labyrinthine Aplasia, Microtia and Microdontia (LAMM) syndrome is characterized by the complete absence of inner ear structures (Michel aplasia), microtia and microdontia. Hypophosphatemic rickets results from defects in the renal tubular reabsorption of filtered phosphate. **Case characteristics**: 13-year-old Indian girl presented with deafness since infancy and progressive wrist widening and genu valgum for last one year. **Observation**: Homozygous novel missense mutation in fibroblast growth factor 3. **Message**: LAMM syndrome and hypophosphatemic rickets may be associated.

Keywords: *Deafness, Fibroblast growth factor receptor-3, Hypophosphatemic rickets.*

Congenital deafness with labyrinthine aplasia (also known as Michel aplasia), microtia, and microdontia (LAMM syndrome, OMIM #610706) is characterized by profound bilateral congenital deafness associated with inner ear anomalies (most often bilateral complete labyrinthine aplasia), type I microtia (typically bilateral), and microdontia. LAMM syndrome is an autosomal recessive condition and has been found in individuals with either homozygous or compound heterozygous *FGF3* mutations [1,2]. The *FGF3* gene encodes fibroblast growth factor 3, a protein that plays a critical role in the embryonic development of the otic placode (which becomes the inner ear) and its differentiation into the vestibular and cochlear structures, the teeth, and external ears. Twelve *FGF3* mutations have been identified in individuals with LAMM syndrome including six missense and six nonsense mutations or small deletions [2].

In this study, we report a 13-year-old girl with LAMM syndrome and progressive hypophosphatemic rickets, which has not been reported earlier, in association with LAMM syndrome.

CASE REPORT

This 13-year-old girl was born to non-consanguineous 37-year-old mother and 37-year-old father. The pregnancy and birth were uneventful. Deafness had been diagnosed in early infancy, and for the past one year, she developed progressive genu valgum and wrist widening and leg pain. Her temporary teeth had just started falling out for the last few months. Except for delayed language, development in all three domains was normal. There was no family history of deafness or skeletal abnormalities. Anthropometry was within normal limits. She presented with type 1 microtia, widely spaced small teeth (***Fig*.1**), and genu valgum. Neurological examination was normal. On investigation, she had profound sensorineural hearing loss; Magnetic resonance imaging of her inner ear showed bilateral complete labyrinthine aplasia (***Fig*.1**). Orthopantogram revealed microdontia, generalized thinning of enamel, and enlarged pulp (***Fig*.1**). An *X*-ray of the patient's pelvis showed generalized osteopenia with an ill-defined pubis. *X*-ray of knees showed fraying, cupping and splaying of metaphyses.

Laboratory analyses of serum revealed following values: inorganic phosphate 2.5 mg/dL, (Normal 3.5-6.6

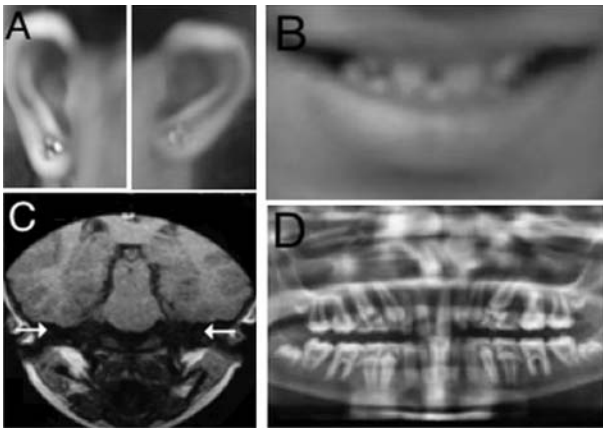

***Fig*. 1** *Clinical findings of the proband: (a) Grade 1 microtia (b) Microdontia (c) Bilateral complete labyrinthine aplasia (d) Microdontia, thin enamel, and increased pulp.*

mg/dL), calcium 8.5 mg/dL; alkaline phosphatase 1755 IU/L; intact-PTH, 55 pg/mL (Normal 9-65 pg/mL); 25-hydoxyvitamin D3, 28 ng/mL (Normal 10-53 ng/mL). Urinary phosphate clearance was increased at 87 mL/min (normal 5–12 mL/min).

Sequencing analysis of the proband revealed a novel homozygous change in *FGF3* (c.534C>G) causing a phenylalanine to leucine substitution at codon 178 (***Web Fig.* 1**). Sequencing analysis of the proband's unaffected parents and sibling revealed that they were all heterozygous for the *FGF3* mutation. Analysis of *FGF23* in the proband showed no variation from the reference sequence.

DISCUSSION

The patient presented here had all three major findings of LAMM syndrome, and was homozygous for an FGF3 mutation, which confirms this diagnosis. Furthermore, the patient presented with genu valgum; osteopenia with an ill-defined pubis; low serum phosphate and elevated alkaline phosphatase despite supplementation with calcium, phosphate, and vitamin D; and an elevated urinary phosphate clearance. These physical findings and laboratory results were consistent with a diagnosis of hypophosphatemic rickets.

Hypophosphatemic rickets is genetically heterogeneous condition and most commonly caused by mutation in PHEX gene, located on X chromosome [3-6]. FGF23 mutation causes autosomal dominant form of hypophosphatemic rickets [7]. We excluded the autosomal dominant form by sequencing FGF23 gene. Possibility of X-linked form was unlikely as most affected patients have early presentation incontrast to this patient who presented with deformities at 13 years of age.

The phenylalanine residue at position 178 is highly conserved among species from fish to primates (***Web Fig.* 1**). The two leucine amino acids located at both sides of phe178 (leu177 and leu179) are implicated in the interaction of FGF3 with its cognate receptor [NCBI Reference Sequence: NG-009016.1]. Thus, it is likely that an amino acid change in this region may alter the receptor-ligand affinity and cause a loss of function, which is confirmative for the pathogenesis in LAMM syndrome.FGF3 and FGF23 are two members of the fibroblast growth factor (FGF) family. In humans, 22 members of the FGF family have been identified, all of which are structurally related signaling molecules [8]. FGF family members possess broad mitogenic and cell survival activities and are involved in a variety of biological processes including embryonic development, cell growth, morphogenesis, tissue repair, and tumor growth and invasion.

In absence of PHEX gene analysis, it is difficult to put causative association between hypophosphatemic rickets and FGF3 mutation. The central role of FGF23 in its etiology and its structural similarity to FGF3 lead us to hypothesize that the mutation found in FGF3 could also be involved in the pathogenesis of hypophosphatemic rickets in this patient. Our hypothesis needs to be substantiated with functional assays on a larger cohort. At present, it seems a mere association with a molecularly confirmed case of LAMM.

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