Oto-Palatodigital Syndrome in a Filipino Child

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ABSTRACT

We present a Filipino male with Otopalatodigital syndrome (OPD) Type I, an X-linked disorder, with characteristic facial and limb anomalies supported by compatible radiographic findings and absence of visceral and severe bone abnormalities.

Key Words: otopalatodigital syndrome type 1, bone abnormalities, X-linked recessive inheritance

Introduction

Taybi in 1962 proposed a new syndrome presenting with "generalized skeletal dysplasia and multiple anomalies" consisting primarily of characteristic facies such as dolicocephaly, hypertelorism and cleft palate, hand and foot abnormalities and, distinctive radiographic findings of dense skull and vertebrae and abnormal modeling of the digital bones.[1]

Dudding et. al, in 1967 described 3 affected male siblings with features that were remarkably similar to the patient described by Taybi and felt that a number of the anomalies comprising this syndrome were singularly striking and should be incorporated into an anatomical, descriptive name appropriate for this syndrome. Thus, they proposed that the name "oto-palato-digital syndrome" be used to describe patients with similar constellation of anomalies.[2]

Clinical Report

Our patient was a 3 year 4 month old male referred to the Genetics Clinic for evaluation and management of his cleft palate.

He was born full term to a 30 year old primigravid mother after an uncomplicated pregnancy. His perinatal history revealed poor Apgar scores and low birth weight of 2 kg (<5th percentile). Broad thumbs, short great toes and cleft of the soft palate were noted at birth.

He had frequent respiratory infections and feeding difficulties during the first 2 years of life and his development was observed to be significantly delayed.

He is the only child of a non-consanguineous couple, a 40 year old Sri Lankan father and a 34 year old Filipino mother (Figure 1). The mother was noted to have frontal bossing, prominent supraorbital ridges and hypertelorism on examination. However, no one in the family had similar features as the mother and the proband.

Physical examination revealed that his height was 80 cm and his weight was 8.85 kg which were both below the 5th percentile for his age and his head circumference was 45 cm (<2SD). Physical findings revealed a dolicocephalic skull with frontal bossing and a prominent occiput, thick eyebrows, downslanted palpebral fissures, ocular hypertelorism, laterally displaced inner canthi which covered the medial part of the sclerae, esotropia, horizontal nystagmus, broad and flat nasal bridge and tip, cupped ears with prominent helices but poorly developed antihelices, incomplete median cleft of the soft palate and micrognathia. Limb anomalies included limitation of extension at the elbows (no dislocation nor fusion on x-ray), broad thumbs, short and flat nailbeds, short fingers (palm length both hands: 6.0 cm (3rd-25th percentile), middle finger length both hands: 3.9 cm (<3rd percentile), camptodactyly of the 2nd-5th fingers, shortened great toes that were proximally inserted and 2nd-5th toe syndactyly on both feet. The rest of the physical and neurologic examinations were normal (Figures 2 A-D).

The patient had a normal 46,XY karyotype. Hearing evaluation by play audiometry showed mild hearing loss on both ears. Ophthalmologic evaluation showed esotropia and nystagmus and corrective lenses were prescribed.

Roentgenographic findings included the following: dense and thick orbital plates of the frontal bones and superior orbital margins, absence of visible pneumatization in the frontal and sphenoid sinuses, small facial bones in relation to the cranium, flattening of the C4-C5 vertebral bodies with slight reversal of the cervical lordotic curve, small iliac bones, shortening of the thumbs and great toes, ulnar deviation of the 2nd digit of both hands and the left 3rd digit of the proximal interphalangeal joints, slight bowing of the tibial bones and left femur and accessory ossification centers at the base of the 2nd metatarsals. Bone aging revealed delayed skeletal maturity at 1year 6 mos old (Figures 3 A-D).

Discussion

Otopalatodigital syndrome (OPD) type I is an X-linked disorder characterized by short stature, mental retardation, characteristic facies such as prominent supraorbital ridges, hypertelorism with down slanted palpebral fissures, broad

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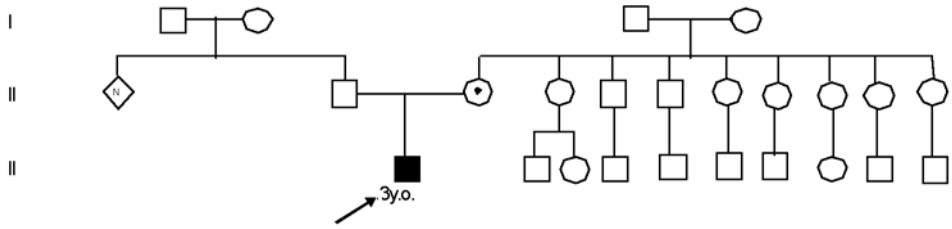
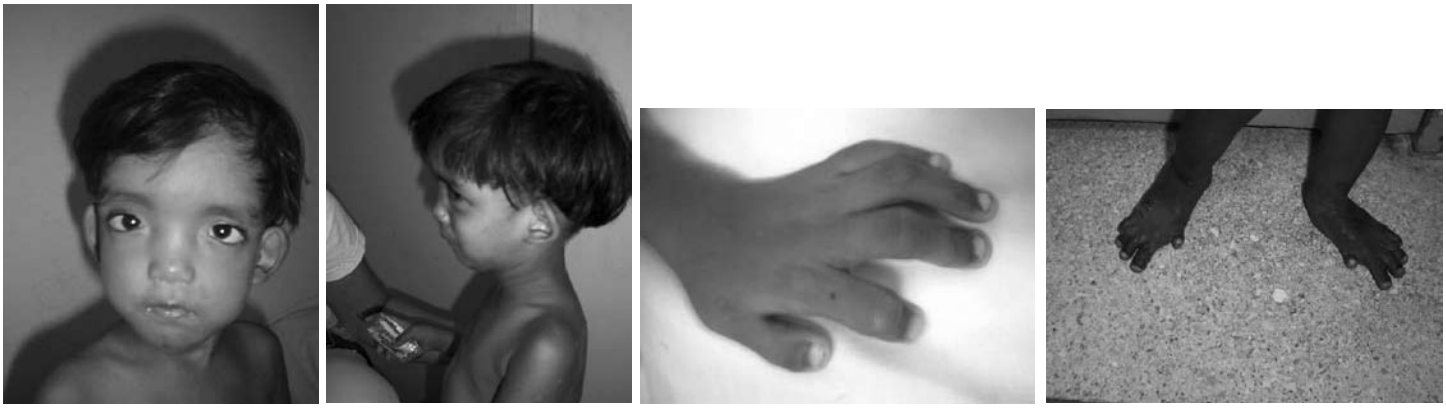
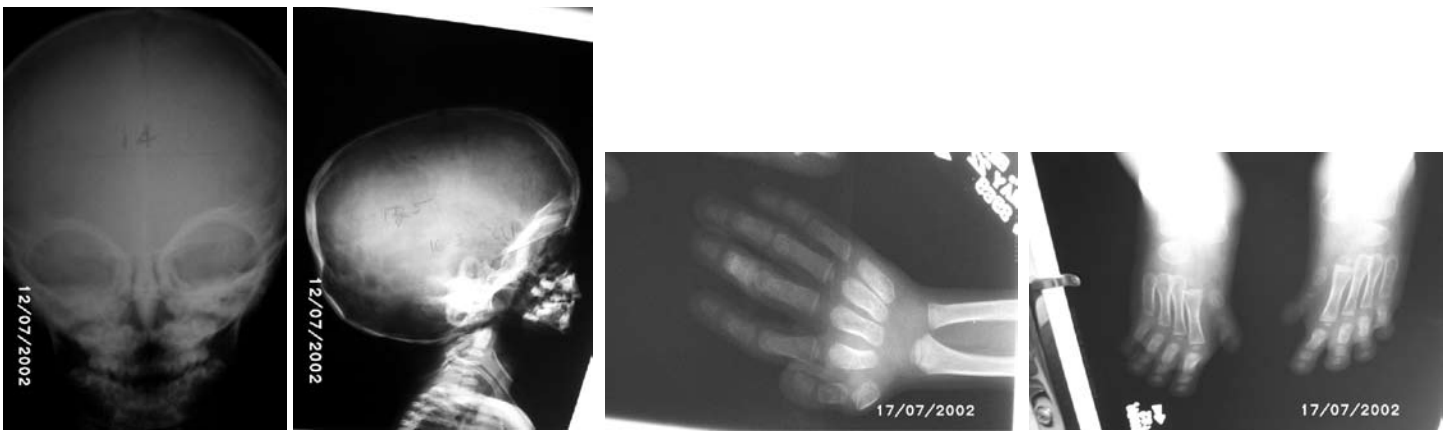


Figure 1. Pedigree of the family



A **B** **C** **D**

Figure 2. A) Dolicocephaly, frontal bossing, hypertelorism with downslanting palpebral fissures, flat nasal bridge. B) Cupped ears and micrognathia C) Broad thumb, flat nailbeds and camptodactyly. D) Short great toes that are very proximally inserted (with permission).



A **B** **C** **D**

Figures 3. A) Dense skull bones. B) Lack of pneumatization in the frontal and sphenoid sinuses. C) Short thumb. D) Short great toes.

nasal bridge, small nose and mouth, cleft palate, abnormal pinnae with hearing loss and various digital anomalies including short, broad distal phalanges of the hands and feet, syndactyly, brachydactyly and short first toes with nail hypoplasia. Typical radiologic findings consist of dense bone at the base of the skull, heavy supraorbital ridges, dense vertebrae with lack of complete closure of some of the neural arches and abnormal modeling of the bones of the upper and lower extremities.[1,3]

A proposed allelic variant of OPD I, termed OPD II is associated with a more severe, frequently lethal phenotype.[4] The pattern of malformation has phenotypic overlap with OPD I but primarily has more severe skeletal changes, such as overlapping fingers, polydactyly, variable syndactyly of hands and feet, narrow chest with wavy clavicles and ribs, bowing of radius, ulna, femur and tibia, small to absent fibula, hypoplastic irregular metacarpals, non-ossified 5th metatarsals, and congenital hip dislocation. The biglycan gene which is involved in bone formation may be responsible for the defective membranous ossification and bone remodelling in this observed phenotype.[5] In addition, brain and visceral abnormalities in the form of omphalocoele, hypospadias, hydronephrosis and hydroureter have been reported as well in this particular type.[6-7]

More recently, it has been suggested that otopalatodigital syndrome types 1 & 2, together with Melnick-Needles syndrome and Frontometaphyseal Dysplasia, sharing many clinical manifestations and a similar mode of inheritance are variants of a single entity – the fronto-oto-palato-digital osteodysplasia.[8] This spectrum of skeletal dysplasias has a possibly common biochemical and/or genetic etiology in their pathogenesis and that, the difference in phenotypic expression is explained by allelic heterogeneity. The gene for these spectrum of these disorders was mapped to Xq28 coding for filamin A. Filamins coordinate and integrate cell signaling and subsequent remodeling of the actin cytoskeleton. Substitutions in the distal portion of the actin-binding domain lead to OPD1 and OPD2. In contrast, only three mutations lead to Melnick-Needles syndrome and mutations that lead to frontometaphyseal dysplasia are the most widely dispersed. The described mutations indicate that they have gain-of-function effects, implicating filamin A in signaling pathways that mediate organogenesis in multiple systems during embryonic development.[9]

Our patient was given the diagnosis of otopalatodigital syndrome type 1 based on the characteristic facial and digital appearance, compatible radiologic findings, the absence of visceral anomalies and severe generalized osteodysplasia. His mother was considered to have the facial changes observed in carrier females. This is consistent with an X-linked pattern of inheritance with variable and intermediate expression in the females. Although more studies are warranted for the further localization of the mutations in OPD 1 gene, molecular studies may be offered to this family for future reproductive risk counseling.

References

1. Taybi H. Generalized Skeletal Dysplasia with Multiple Anomalies. Am J Roentgen. 1962; 88:450-457.
2. Dudding B, Gorlin RJ, Langer LO. The Otopalatodigital Syndrome: a new symptom complex consisting of deafness, dwarfism, cleft palate, characteristic facies, and a generalized bone dysplasia. Am J Dis Child 1967; 113:214-221.
3. Jones, Kenneth L. Smith's Recognizable Patterns of Human Malformation, 5th ed. W. B. Saunders Company. 1997. 270-271.
4. Fitch N, Jequier S, Gorlin R. The Otopalatodigital Syndrome, proposed type II. Am J. Med Genet. 1983; 15: 655-664.
5. Savarirayan R, Cormier-Daire V, Unger S, et al. Otopalatodigital Syndrome type II: report of three cases with further delineation of the chondro-osseous morphology. Am J Med Genet. 2000; 95:193-200.
6. Stratton R, Bluestone D. Otopalatodigital Syndrome type II with X-linked Cerebellar Hypoplasia/ Hydrocephalus. Am J Med Genet 1991; 41:169-172.
7. Young K, Barth CK, Moore C, et. al. Otopalatodigital syndrome type II associated with omphalocoele: report of three cases. Am J Med Genet. 1993; 45:481-487.
8. Verloes A, Lesenfants S, Barr M, Grange DK, Journel H, Lombet J, et al. Fronto-Otopalatodigital Osteodysplasia: clinical evidence for a single entity encompassing Melnick-Needles syndrome, Otopalatodigital syndrome types 1 and 2, and frontometaphyseal dysplasia. Am J Med Genet. 2000; 90: 407-422.
9. Robertson SP, Twigg SR, Sutherland-Smith AJ, et al. OPD-spectrum Disorders Clinical Collaborative Group. Localized mutations in the gene encoding the cytoskeletal protein filamin A cause diverse malformations in humans. Nat Genet. 2003; 33: 487-491.