Oto-Palatodigital Syndrome in a Filipino Child

Mary Anne D. Chiong1,2, Eva Maria C. Cutiongco-de la Paz1,2

1Department of Pediatrics, College of Medicine, and Philippine General Hospital, University of the Philippines Manila; 2Institute of Human Genetics, National Institutes of Health, University of the Philippines Manila

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 vertebral bone and abnormal modeling of the digital bones.

Dudding et al, in 1967 described 3 affected male siblings with features that were remarkably similar to the patient described by Taybi and 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.

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. 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 palpebral fissures 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 naillbeds, 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 1 year 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
Figure 1. Pedigree of the family

Figure 2. A) Dolicoccephaly, 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).

Figure 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,
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.