Clinical Case Reports

Open Access

CASE REPORT

Extended phenotypes in a boy and his mother with oto-palato-digital-syndrome type II

Ali Al Kaissi[1,2], Raimund Kraschl[3], Wilhelm Kaulfersch [3], Franz Grill[2] & Rudolf Ganger[2]

[1]First Medical Department, Ludwig Boltzmann Institute of Osteology, at the Hanusch Hospital of WGKK and, AUVA Trauma Centre Meidling, Hanusch Hospital, Vienna, Austria
[2]Paediatric Department, Orthopaedic Hospital of Speising, Vienna, Austria
[3]Department of Pediatric and Neonatology, Klagenfurt Clinic, Klagenfurt, Austria

Correspondence
Ali Al Kaissi, Pediatric Department, Orthopedic Hospital of Speising- Speisinger Straße 109, A-1130 Vienna, Austria.
Tel.: +43 1 801 82 – 1260; Fax: +43 1 801 82 – 1494; E-mail: ali.alkaissi@oss.at

Funding Information
No sources of funding were declared for this study.

Received: 14 January 2015; Revised: 7 April 2015; Accepted: 21 April 2015

Clinical Case Reports **2015; 3(9): 762–766**

doi: 10.1002/ccr3.317

Key Clinical Message

We describe additional phenotypic features in a boy and his mother. Both manifested the phenotypic/genotypic correlation of oto-palato-digital syndrome type II. The mother's radiographs showed wormian bones of the skull, and paranasal bossing, her feet showed bilateral fusion of the cuboid with the lateral cuneiform bone with subsequent development of metatarsus varus associated with dysplastic distal phalanges.

Keywords

Extended phenotype, FLNA gene Mutation, oto-palato-digital type II, skeletal changes.

Introduction

Oto-palato-digital (OPD II) syndrome is characterized by hearing impairment, cleft palate, hypertelorism downslanting palpebral fissures, micrognathia, posteriorly rotated ears, a prominent forehead and microstomia [1]. In the limbs, there is flexed overlapping fingers, syndactyly, notched or bifid terminal phalanges, postaxial polydactyly, and short halluces and thumbs. Radiographs showed hip dislocations, dense bones, curved or wavy short ribs, sloping clavicles, and spread out ilia with thick ischia and flat acetabulae [2–4]. As the child grows, the facial features become less severe, the bone curvature improves and the osteosclerosis of the long bones lessens [5, 6]. Robertson et al. [6] mapped the gene to Xq28 suggesting allelism to OPD type 1. They also showed that female carriers had skewed X inactivation and demonstrated. Robertson et al. [7] demonstrated that OPD II is caused by mutations in the coding region of the filamin A gene. Verloes et al. [8] noted the overlap between OPD syndromes and Melnick-Needles, thus he suggested the term fronto-oto-palatodigital osteodysplasia for this group of syndromes.

Clinical Reports

The child was referred to our department for clinical assessment. He was the first child of nonconsanguineous parents. He was born full term at 41 weeks and manifested perinatal asphyxia (APGAR 4/6/7) because of respiratory insufficiency. He presented with the characteristic facial dysmorphic features of OPD, prominent forehead, flat nasal bridge, hypertelorism, downslanting palpebral fissures, short nose, long philtrum, small mouth, micrognathia and cleft palate, multiple contractures along the elbows, hips, knees, and ankle joints, respectively (Fig. 1). Profile of the face showed low-set crumpled ears, and the hands showed flexion contractures of the interphalangeal joints with short broad metacarpals and broad terminal phalanges with overlapping of the fingers and duplication of the fifth fingers bilaterally (Fig. 2). Lateral skull radiograph showed a large cranium in relation to the face, severe demineralization of the calvaria and the skull bones associated with a large anterior fontanel and hypoplastic mandible (Fig. 3). Anteroposterior (AP) radiograph of the hands showed flexion contractures of the interphalangeal joints with short broad metacarpals and phalanges

and overlapping of the fingers, duplication of the fifth finger bilaterally, defective ossification of the first fingers with subsequent development of delta phalanges of first, second, and fifth metacarpophalanges. The metacarpophalanges are broad and short with hypoplastic and bowing of the radius and ulna, and subluxated elbows (Fig. 4).

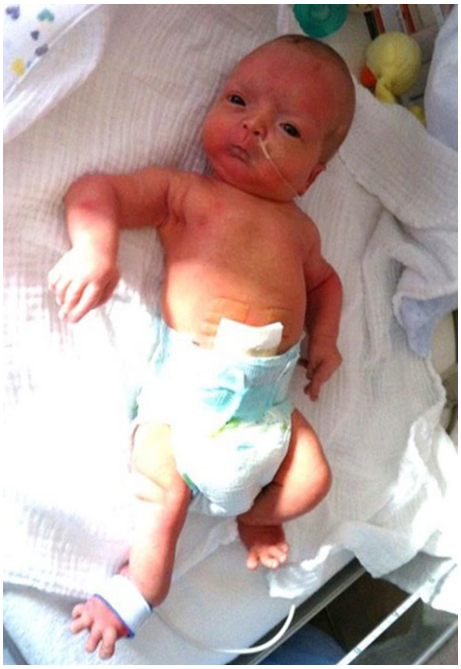

Figure 1. Characteristic facial dysmorphic features of OPD, prominent forehead, flat nasal bridge, hypertelorism, downslanting palpebral fissures, short nose, long philtrum, small mouth, micrognathia and cleft palate, multiple contractures along the elbows, hips, knees and ankle joints, respectively.

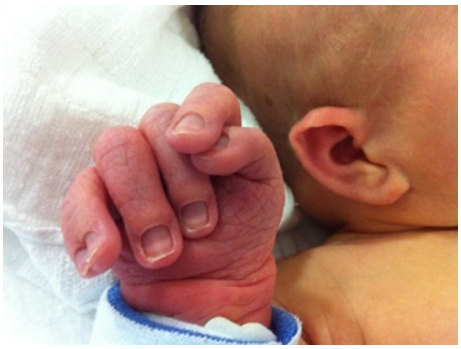

Figure 2. Profile of the face showed low-set crumpled ears, and the hands showed flexion contractures of the interphalangeal joints with short broad metacarpals and broad terminal phalanges with overlapping of the fingers and duplication of the fifth fingers bilaterally.

AP chest radiograph showed thoracic hypoplasia, delayed ossification of the vertebral bodies, coronal clefts, and dysplastic clavicles with gracile, wavy, and thin ribs (Fig. 5). AP radiograph of the lower limbs at the age of 1 showed severe anatomical distortion of the acetabulofemoral structures with subsequent dislocation associated with delayed ossification of the pubic bones and sacroiliac hypoplasia with bowing of the femora, there is bilateral bowing of the tibiae and bilateral fibular aplasia (remnants of fibular cartilaginous anlage) causing effectively the development of bilateral dislocated ankle joints and the feet are in vulgus position (Fig. 6). Examination of the 25-years-old mother revealed; Short stature, pugilistic face, and nasal tonation. Her skull radiographs showed unusual ossification of the frontal sinus, calcification of the calvaria but wormain bones along the

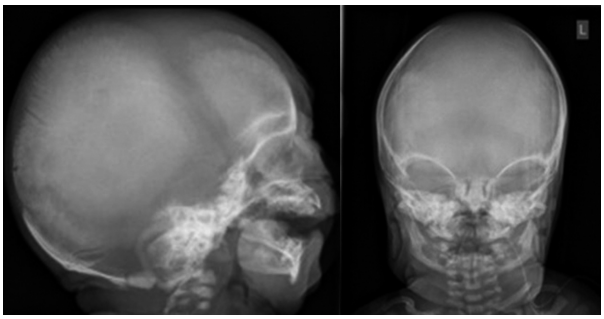

Figure 3. Lateral and AP skull radiographs showed large cranium in relation to the face, severe demineralization of the calvaria and the skull bones associated with large hypomineralized anterior fontanel and hypoplastic mandible.

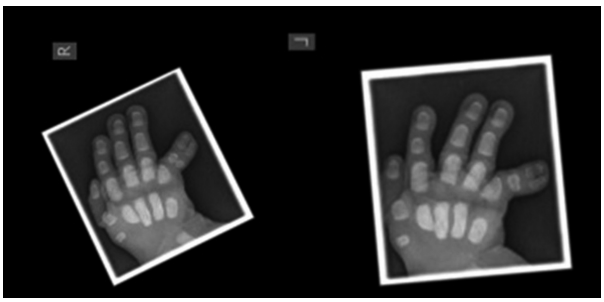

Figure 4. AP hand radiographs showed flexion contractures of the interphalangeal joints with short broad metacarpals and phalanges and overlapping of the fingers, duplication of the fifth finger bilaterally, defective ossification of the first fingers with subsequent development of delta phalanges of the first, second, and fifth metacarpophalanges. The metacarpophalanges are broad and short with hypoplastic and bowing of the radius and ulna, and sub-luxated elbows.

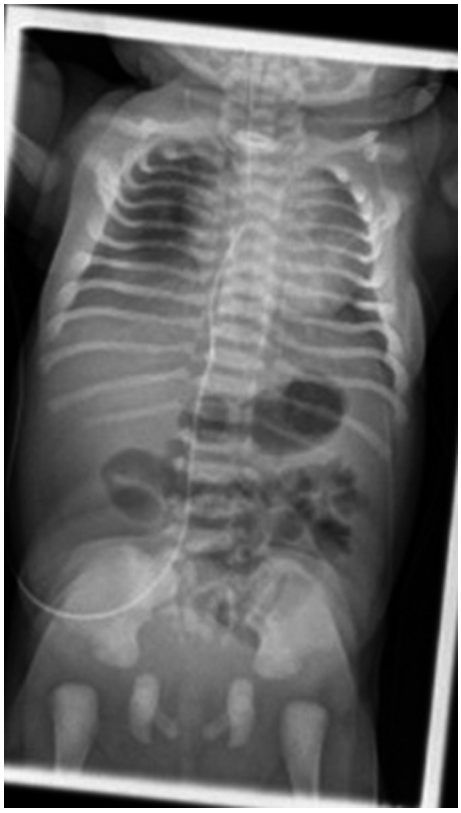

Figure 5. AP chest radiograph showed thoracic hypoplasia, delayed ossification of the vertebral bodies, coronal clefts, and dysplastic clavicles with gracile, wavy, and thin ribs.

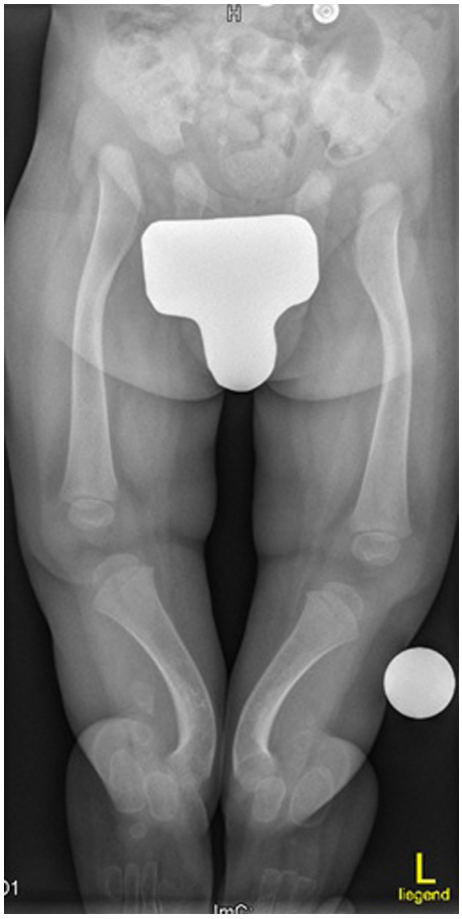

Figure 6. AP radiograph of the lower limbs at the age of 1 year showed severe anatomical distortion of the acetabulofemoral structures with subsequent dislocation associated with delayed ossification of the pubic bones and sacroiliac hypoplasia with bowing of the femora, there is bilateral bowing of the tibiae and bilateral fibular aplasia (remnants of fibular cartilaginous anlage) causing effectively the development of bilateral dislocated ankle joints and the feet are in vulgus position.

posterior skull aspect were present (Fig. 7). AP radiograph of the feet radiograph showed bilateral fusion of the cuboid with the lateral cuneiform bone (arrow) with subsequent development of metatarsus varus with dysplastic distal phalanges and a broad first ray of the great toe, though the 2, 3, 4, and 5th toes are dysplastic.

Molecular Genetic Analysis of the FLNA Gene

The *FLNA gene* exons and Introns/exons boundaries were screened by next-generation sequencing on an Ion Torrent apparatus, by using a gene panel approach. The results were validated by PCR amplification of selected exons followed by bidirectional fluorescent direct sequencing (Sanger)Mutation c.635A>T was present in hemizygosity in exon 4 of the *FLNA* gene in the child′s DNA. The same mutation has been identified in heterozygosity in the *FLNA* gene in the DNA of the child′s mother. The heterozygous A-to-T transition at nucleotide 635 in exon 4, resulted in an Aspartic acid (GAG)-to-Valine (GTC) substitution at codon 212 (Asp212 Val).

Treatment

The reconstruction of the lower limbs will be performed via operation of tibia with resection of the fibular cartilagineous anlage. This will take place in June 2015 in Speising orthopaedic hospital. Of course, no interventions until a dynamic cervical spine MRI assesses the dysplastic C1-2. Additional surgical procedures are warranted, but are not planned at this point. Both Hips and ankle joints need further observation and assessment.

Discussion

Preis et al. described two cases of unrelated boys with OPD II who showed missing or hypoplastic fibulae,

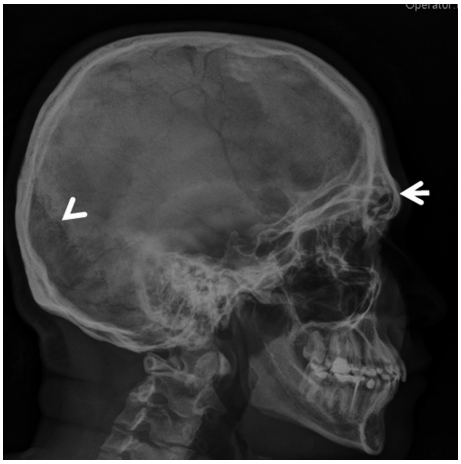

Figure 7. Lateral skull radiographs of the mother unusual ossification and bossing of the frontal sinus (arrow), calcification of the calvaria but wormain bones along the posterior skull aspect were present (arrow head).

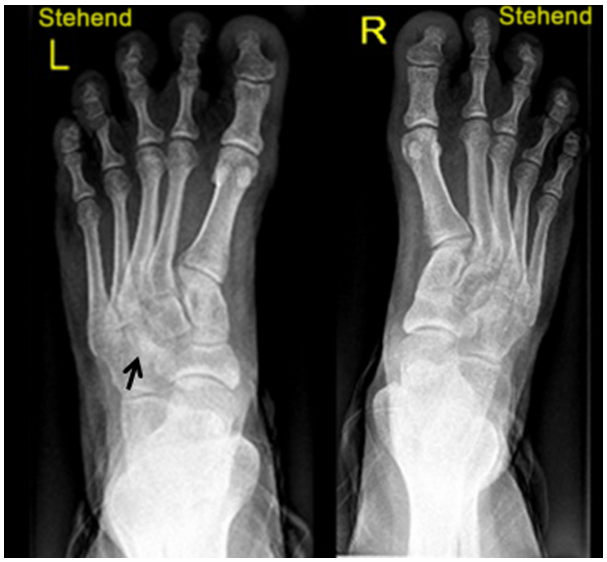

Figure 8. AP feet radiograph showed bilateral fusion of the cuboid with the lateral cuneiform (arrow) bone with subsequent development of metatarsus varus with dysplastic distal phalanges and broad first ray of the great toe, though the 2, 3, 4, and 5th toes are dysplastic.

sclerosis of the skull base, widely spaced eyes, antimongoloid slant, and the facial appearance was distinguished by a prominent forehead. The mother of one of the boys manifested a large skull with prominent forehead, hypertelorism, low-set ears, high-arched palate, and retrogenia. She also had hearing loss and mild flexion contracture of the right elbow. On radiologic examination, the maxillary sinuses were absent, and the bone density of the skull bones and long bones was increased. They found reports of 20 fully affected patients and 9 partially affected mothers, including their patient [9].

Distinctive abnormalities in our patient included a constellation of noteworthy features; characteristic facial dysmorphic features of OPD, defective ossification of the clavaria, large fontanelles, prominent forehead, flat nasal bridge, hypotelorism, downslanting palpebral fissures, low set-"crumpled" ears, short nose, long philtrum, small mouth, micrognathia, and cleft palate. Interestingly, multiple joint dislocations of elbows, hips, knees and ankle joints were notable. In addition there was bilateral and symmetrical fibular aplasia with remnants of fibular cartilaginous anlage causing valgus position of the feet, noteworthy features in the mother include; short stature, semipugilistic face, nasal tonation, small hands, and feet. Radiographs of the mother showed bilateral fusion of the cuboid with the lateral cuneiform bone with subsequent development of metatarsus varus with dysplastic distal phalanges and broad first ray of the great toe, through the 2, 3, 4, and 5th toes were dysplastic. Her skull radiographs showed unusual ossification of the mastoids, wormian bones, and paranasal bossing. The overall clinical and radiographic phenotypes in our patients are to certain extent expanding the clinical spectrum in the OPD II syndrome. The specific missense mutation encountered appears not to have been reported before but is located in the calponin homology domain 2(CH2) and affects an Aspartic Acid residue conserved in all three filamin paralogs in humans and is not reported in controls of different variant databases (Exome Variant Server;dbSNP).

Acknowledgements

We thank L. Bonafé, MD, PhD, Professor and Director of the Laboratory, Hospitalier Universitaire Vaudois, Lausanne, Switzerland for her help in confirming the diagnosis through performing the Molecular Genetic Analysis in this family.

Conflict of Interest

Authors declare no conflict of interest.

References

1. Ogata, T., N. Matsuo, G. Nishimura, and H. Hajikano. 1990. Oto-palato-digital syndrome, type II: evidence for defective intramembranous ossification. Am. J. Med. Genet. 36:226–231.
2. Andre, M., J. Vigneron, and F. Didier. 1981. Abnormal facies, cleft palate and generalised dysostosis: a lethal X-linked syndrome. J. Pediatr. 98:747–752.
3. Brewster, T. G., R. S. Lachman, D. C. Kushner, L. B. Holmes, R. J. Isler, and D. L. Rimoin. 1985. Oto-palato-digital

syndrome, type II—an X-linked skeletal dysplasia. Med. Genet. 20:249–254.
4. Dudding, B. A., R. J. Gorlin, and L. O. Langer. 1967. The oto-palatodigital syndrome. A new symptom-complex consisting of deafness, dwarfism, cleft palate, characteristic facies, and a generalized one dysplasia. Am. J. Dis. Child. 113:214–221.
5. Robertson, S., T. Gunn, B. Allen, C. Chapman, and D. Becroft. 1997. Are Melnick-Needles syndrome and otopalatodigital syndrome type II allelic? Observations in four-generation kindred. Am. J. Med. Genet. 71:341–347.
6. Robertson, S. P., S. Walsh, M. Oldridge, T. Gunn, D. Becroft, and A. O. Wilkie. 2001. Linkage of otopalatodigital syndrome type 2 (OPD2) to distal Xq28: evidence for allelism with OPD1. Am. J. Hum. Genet. 69:223.
7. Robertson, S. P., S. R. Twingg, A. L. Sutherland-Smith, V. Biancalana, R. J. Gorlin, D. Horn, et al. 2003. Localized mutations in the gene encoding the cytoskeletal protein filamin A cause diverse malformations in humans. Nat. Genet. 33:487–491.
8. Verloes, A., S. Lesenfants, M. Barr, D. K. Grange, H. Journel, J. Lombert, et al. 2000. Fronto-otopalatodigital osteodysplasia: clinical evidence for a single entity encompassing Melnick-Needles syndrome, otopalatodigital syndrome types 1 and 2, and frontometaphyseal dyplasia. Am. J. Med. Genet. 90:407–422.
9. Preis, S., H. Kemperdick, and F. Majewski. 1994. Oto-palato-digital syndrome type II in two unrelated boys. Clin. Genet. 45:154–161.