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Wide-spread cone-shaped epiphyses in two Saudi siblings with Ellis-van Creveld syndrome



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ABSTRACT

INTRODUCTION: Ellis-van Creveld (EVC) syndrome is one of the rarest ciliopathy syndromes. It is caused by mutations of the *EVC* and *EVC2* genes which encode the EVC proteins present in the basal body of the primary cilium.

PRESENTATION OF CASES: We report on a Saudi family with two affected children. Gene analysis revealed a homozygous c.2T >A in exon 1 of the *EVC* gene. The most interesting finding in our patients was the wide – spread cone-shaped epiphyses in the hands and feet.

DISCUSSION: Although cone-shaped epiphyses is a known feature of EVC syndrome, it usually limited to the middle or proximal phalanges. The wide-spread cone-shaped epiphyses seen in our patients have not been previously reported.

CONCLUSION: EVC syndrome is very rare in the Middle East. We report on the first Saudi family with EVC syndrome confirmed by gene analysis. The most unique finding in our patients was the wide-spread cone-shaped epiphyses in the hands and feet. The abnormality is probably related to abnormal Indian hedgehog signaling in the primary cilium.

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1. Introduction

Ciliopathies are a group of syndromes caused by genetic mutations encoding proteins related to the formation or function of the embryonic primary cilium [1]. The primary cilium is composed of three parts: a basal body (attached to the actin network of the cell), an axoneme (projecting microtubules) and a ciliary membrane (covering the axoneme) [2]. The primary cilium is the site of hedgehog signal transduction which includes Sonic hedgehog (involved in limb patterning and the pathogenesis of ulnar polydactyly) and Indian hedgehog (involved in the coordination of chondrocyte proliferation and differentiation) [2,3].

Ellis-van Creveld (EVC) syndrome (also known as chondroectodermal dysplasia, MIM 225500) is one of the rarest ciliopathies. It is inherited as autosomal recessive and is caused by mutations of the *EVC* and *EVC2* genes which encode the EVC proteins present in the basal body of the primary cilium. The syndrome is known to be prevalent in Amish, Brazilian and Ashkenazi Jewish populations [4,5]. Outside these populations, the birth prevalence has been estimated to be 7/1,000,000 live births [6].

The EVC syndrome is characterized by disproportionate short limb dwarfism, ulnar polydactyly, cone-shaped epiphyses, capitate-hamate fusion, hypoplasia of the distal phalanges, dysplastic nails, oligodontia, multiple frenulae, conical teeth, and short ribs. About two-thirds of patients have cardiac defects [7,8]. A characteristic defect in the lateral aspect of the proximal tibial epiphysis (leading to genu valgum) has also been reported [8].

Although cone-shaped epiphysis is a known radiological feature of EVC syndrome, it is usually limited to the middle or proximal phalanges. In this report, we describe two Saudi siblings with EVC syndrome and a very unusual wide-spread cone-shaped epiphyses of the hands and feet. This finding has not been previously reported. Furthermore, our report represents the first Saudi family with EVC syndrome confirmed by gene analysis. The work has been reported in line with the SCARE criteria [9].

2. Case reports

Two Saudi siblings presented to the senior author (MMA) with classic features of EVC syndrome. The parents were first degree cousins and had no abnormalities. The clinical and radiological features of their two affected children are summarized in [Table 1](#); and are demonstrated in [Figs. 1–6](#). Of interest is the presence of wide-spread cone-shaped epiphyses in the hands and feet ([Figs. 3–6](#)).

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Table 1
Clinical and Radiological Features in Two Saudi Siblings with Evc Syndrome.

Feature	Case 1 (Female, 5 years old)	Case 2 (Female, 6 years old)
Disproportionate short limb dwarfism	Yes	Yes
Narrow chest	Yes	Yes
Cardiac defects	Atrial septal defect	Atrial septal defect
Genu valgum	Yes	Yes
Nail dystrophy	All digits	All digits
Oral features	Oligodontia, conical teeth, multiple frenulae	Oligodontia, conical teeth, multiple frenulae
Brachydactyly	In the hands	In the hands
Postaxial polydactyly	Both hands and both feet (The polydactyly of hands were excised prior to presentation to our clinic)	Both hands
Radiological features:		
- Ribs	Short ribs	Short ribs
- Proximal tibia	Defect in the lateral aspect of the proximal tibial epiphysis and exostosis of the medial proximal tibia	Defect in the lateral aspect of the proximal epiphysis
- The hips	Short femoral necks	Short femoral necks
- The hands	Generalized mild brachydactyly, postaxial polydactyly, hypoplasia of distal phalanges, and wide-spread cone-shaped epiphyses (See Figs. 3 and 4). No capitate-hamate fusion	Generalized moderate brachydactyly, postaxial polydactyly, hypoplasia of the distal phalanges, and wide-spread cone-shaped epiphyses (See Figs. 5 and 6). Capitate-hamate fusion was seen in the left wrist.
- The feet	Post-axial polydactyly, cone-shaped epiphyses of all proximal phalanges, hypoplasia of the distal phalanges.	Cone-shaped epiphyses of all proximal phalanges, hypoplasia of the distal phalanges.



Fig. 1. Demonstration of the hypoplastic nails (Case 2). Also note the brachydactyly and postaxial polydactyly of the hands.

All coding exons of the *EVC* and *EVC2* genes were amplified by PCR and the amplified products were then sequenced and analyzed for sequence variations. DNA analysis revealed a homozygous c.2T >A trans-version in exon 1 of the *EVC* gene in both affected children. Parents were heterozygous for the same mutation. This change converts the start codon from ATG to AAG and will disrupt the translation of the *EVC* protein. The mutation is known to be a disease-causing mutation [10].

3. Discussion

The *EVC* syndrome is very rare and is worth reporting. Furthermore, our report aims to report on the first Saudi family with *EVC* syndrome confirmed by gene analysis. The largest cohort (371 patients from 265 family) of various ciliopathy syndromes was recently reported; including families from Saudi Arabia [11]. In that cohort, none of the patients had mutations of the *EVC/EVC2* genes; confirming the rarity of the *EVC* syndrome [11].

The most interesting finding in our patients was the wide-spread cone-shaped epiphyses in the hands and feet. The *EVC* protein is part of the basal body of the primary cilium which is the site of Sonic and Indian hedgehog signaling. Experimentally, abnormalities of the *EVC* protein lead to disruption of hedgehog signaling [10,12]. The Indian hedgehog is involved in the coordination of chondrocyte proliferation and differentiation; and this is the most likely cause of cone-shaped epiphyses.

Although genotype-phenotype relationships are controversial in *EVC* syndrome, certain mutations are known to be hypomorphic; and these mutations cause a less severe phenotype [13,14]. In patients with these hypomorphic mutations, the cone-shaped epiphyses are either absent or seen in a single phalanx [13,14]. We also did an extensive literature search on the distribution of cone-shaped epiphyses in all other reported cases of *EVC* syndrome and did not find any cases with wide-spread cone-shaped epiphyses similar to our cases. In previous cases of *EVC* syndrome, the cone-shaped epiphyses were seen in either in the proximal or middle phalanges [6,15,16]. In our second case, cone-shaped epiphyses were seen in all of the phalanges (proximal, middle, and distal phalanges) as well as all of the metacarpals (see Fig. 5).

It is important to realize that cone-shaped epiphyses are also seen in other ciliopathy syndromes [17–21]. This is not surprising because the hedgehog signaling is abnormal in all ciliopathy syndromes. Furthermore, Al-Qattan [19] reviewed the literature on craniofacial syndromes with cone-shaped epiphyses and these included: trichorhinophalangeal syndrome, cleidocranial dysplasia, cartilage-hair hypoplasia, and Albright hereditary osteodystrophy. All these syndromes have in common abnormalities of embryonic bone and cartilage development. The presence of a defect in the lateral aspect of the proximal tibial epiphysis is highly characteristic of *EVC* syndrome [8]. This is also considered as an epiphyseal abnormality; and it was present in our patients. Tsuji et al. [22] demonstrated that *EVC* mRNA was present in the



Fig. 2. Demonstration of the genu valgum and the characteristic defect of the lateral aspect of the proximal tibial epiphyses (Case 2).



Fig. 3. The hands in Case #1. Note the wide-spread cone-shaped epiphyses of all phalanges.



Fig. 4. The feet in Case #1. Note the cone-shaped epiphyses of all proximal phalanges.



Fig. 5. The hands in Case #2. Note the cone-shaped epiphyses of all phalanges and metacarpals. There is also capitulum-hamate fusion in the right hand.



Fig. 6. The feet in Case #2. Note the cone-shaped epiphyses of all proximal phalanges.

chondrocytes of the tibial epiphyseal growth plate. The expression of *EVC* in the growth plates of the phalanges and metacarpals has not been studied and is worth exploring.

4. Conclusion

EVC syndrome is very rare in the Middle East. We report on a Saudi family with two affected children. Gene analysis revealed a homozygous c.2T>A in exon 1 of the *EVC* gene. The most interesting finding in our patients was the wide-spread cone-shaped epiphyses in the hands and feet. This finding has not been previously reported. The epiphyseal abnormality is probably related to abnormal Indian hedgehog signaling in the primary cilium.

Conflict of interest

None.

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Ethical approval

The study was approved by the research committee, National Hospital (Care), Riyadh, Saudi Arabia.

Consent

Written informed consent was obtained from the parents for publication of this case report. A copy of the written consent is available for review by Editor-In-Chief of this journal on request.

Author's contributions

Both authors contributed significantly and in agreement with the content of the manuscript. Both authors participated in the literature review, data collection and writing of the final draft.

Guarantor

M M Al-Qattan.

References

- [1] A.M. Waters, P.L. Beales, Ciliopathies: an expanding disease spectrum, *Pediatr. Nephrol.* 26 (2011) 1039–1056.
- [2] M.W. Al-Kattan, M.M. Al-Qattan, S.A. Bafaqeh, The pathogenesis of the clinical features of oral-facial-digital syndrome type I, *Saudi Med. J.* 36 (2015) 1277–1284.
- [3] M.M. Al-Qattan, M.I. Al-Motairi, The pathogenesis of ulnar polydactyly in humans, *J. Hand Surg. Eur. Vol.* 38 (2013) 934–939.
- [4] V.L. Ruiz-Perez, S.E. Ide, T.M. Storm, et al., Mutations in a new gene in/Ellis-van-Creveld syndrome and Weyers acrocentric dysostosis, *Nat. Genet.* 24 (2000) 283–286.
- [5] M. Goldzicka, S. Patnala, M.G. Hirshman, et al., A new gene *EVC2*, is mutated in Ellis-van Creveld syndrome, *Mol. Genet. Metab.* 77 (2002) 291–295.
- [6] L. Kayal, S. Jayachandran, K.S. Singh, Chondroectodermal dysplasia (Ellis-van Creveld syndrome): a case report with dental considerations and review of literature, *Intern. Med. Open Access* 2 (2012) 1, <http://dx.doi.org/10.4172/2165-8048.1000104>.
- [7] V.A. McKusick, J.A. Egeland, R. Eldridge, D.E. Krusen, Dwarfism in the Amish I: the Ellis-van Creveld syndrome, *Bull. Johns Hopkins Hosp.* 115 (1964) 306–336.
- [8] G. Baujat, M. Le Merrer, Ellis-van Creveld syndrome, *Orphanet J. Rare Dis.* 2 (2007) 27, <http://dx.doi.org/10.1186/1750-1172-2-27>.
- [9] R.A. Agha, A.J. Fowler, A. Soetta, I. Barai, S. Rajmohan, D.P. Orgill, SCARE steering group, A protocol for the development of reporting criteria for surgical case reports. The SCARE statement, *Int. J. Surg.* 27 (2016) 187–189.
- [10] M. Valencia, P. Lapunzina, D. Lim, et al., Widening the mutation spectrum of *EVC* and *EVC2*: ectopic expression of Weyers variants in NIH 3T3 fibroblasts disrupts hedgehog signaling, *Hum. Mutat.* 20 (2009) 1667–1675.
- [11] R. Shaheen, K. Szymanska, B. Basu, et al., Characterizing the morbid genome of ciliopathies, *Genome Biol.* 17 (2016) 242, <http://dx.doi.org/10.1186/S13059-016-1099-5>.

- [12] V.L. Ruiz-Perez, J.A. Goodship, Ellis-van Creveld syndrome and Weyers acrodistal dysostosis are caused by cilia-mediated diminished response to hedgehog ligands, *Am. J. Med. Genet. Part C Semin. Med. Genet.* 151 (2009) 341–351.
- [13] H. Ulucan, D. Gul, J.C. Sapp, et al., Extending the spectrum of Ellis-van Creveld syndrome: a large family with a mild mutation in the EVC gene, *BMC Med. Genet.* 9 (2008) 92, <http://dx.doi.org/10.1186/1471-2350-9-92>.
- [14] W. Shen, D. Han, J. Zhang, H. Zhao, H. Feng, Two novel heterozygous mutations of EVC2 cause a mild phenotype of Ellis-van Creveld syndrome in a Chinese family, *Am. J. Med. Genet. Part A* 155 (2011) 2131–2136.
- [15] M. Amin, A. Swaleh, Ellis-van Creveld syndrome, *Pak. J. Radiol.* 23 (2013) 39–42.
- [16] K. De Jongh, F.M. Vanhoenacker, S. Van de Perre, G. Mertens, M.M. De Schepper, Chondroectodermal dysplasia, *J. Belgian Radiol. (JBR-BTR)* 89 (2006) 124–125.
- [17] F. Maizer, R.M. Suldino, M.B. Ozonoff, H. Minagi, Familial nephropathy associated with retinitis pigmentosa: cerebellar ataxia and skeletal abnormalities, *Am. J. Med.* 49 (1970) 556–562.
- [18] D.S. Ellis, J.R. Heckenlively, C.L. Martin, et al., Leber's congenital amaurosis associated with familial juvenile nephronophthisis and cone-shaped epiphyses of the hands (the saline-Mainzer syndrome), *Am. J. Ophthalmol.* 97 (1984) 233–239.
- [19] M.M. Al-Qattan, Cone-shaped epiphyses in the toes and trifurcation of the soft palate in oral-facial-distal syndrome type 1, *Br. J. Plast. Surg.* 51 (1998) 476–479.
- [20] W. Tory, C. Rousset-Rouvriere, M.C. Gubler, et al., Mutations of NPHP2 and NPHP3 in infantile nephronophthisis, *Kidney Int.* 75 (2009) 839–847.
- [21] A.M. Lehman, P. Eudonx, D. Doherty, et al., Co-occurrence of Joubert syndrome and Jeune asphyxiating thoracic dystrophy, *Am. J. Med. Genet. A* 6 (2010) 11411–11419.
- [22] J. Tsuji, H. Nakamura, A. Hirata, T. Yamamoto, Expression of Ellis-van Creveld (EVC) gene in the rat tibial growth plate, *Anat. Rec. Part A* 279 (2004) 729–735.

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