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Non lethal Raine syndrome and differential diagnosis

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ABSTRACT

Raine syndrome is a rare autosomal recessive bone dysplasia characterized by characteristic facial features with exophthalmos and generalized osteosclerosis. Amelogenesis imperfecta, hearing loss, seizures, and intracerebral calcification are apparent in some affected individuals. Originally, Raine syndrome was originally reported as a lethal syndrome. However, recently a milder phenotype, compatible with life, has been described. Biallelic variants in*FAM20C,* encoding aGolgi casein kinase involved in biomineralisation, have been identified in affected individuals.

We report here a consanguineous Moroccan family with two affected siblingsa girl aged 18 and a boy of 15years. Clinical features, including learning disability, seizures and amelogenesis imperfecta, initially suggested a diagnosis of Kohlschutter-Tonz syndrome. However,a novel homozygous *FAM20C*variantc.676T > A, p.(Trp226Arg) was identified in the affected siblings. Our report reinforces that Raine syndrome is compatible with life, and that mild hypophosphatemia and amelogenesis imperfecta are key features of the attenuated form.

1. Introduction

Raine syndrome (MIM # 259775) is an autosomal recessive disorder, defined by characteristic facial features (midface hypoplasia, hypoplastic nose, exophthalmos, and low set ears), and generalized osteosclerosis. Additional features reported in some affected individuals include a wide fontanelle, intracranial calcification, sensorineural hearing loss, neurodevelopmental delay, epilepsy, and amelogenesis imperfecta. Recently, cerebellar hypoplasia and pachygyria have been reported as part of the phenotype (Seidahmed et al., 2015).It is estimated to affect less than 1 in one million individuals (Faundes et al., 2014). Most cases have been lethal in the newborn period. However, eight cases of Raine syndrome have been reported to survive intochildhood or adulthood (Fradin et al., 2011; Rafaelsen et al., 2013; Simpson et al., 2009; Acevedo et al., 2015). The rarity of the non-lethal phenotype means that the full phenotypic spectrum is unlikely to have been fully delineated. Notably, it was recently emphasized that amelogenesis imperfecta is a key diagnostic feature of the non-lethal form (Acevedo et al., 2015). Amelogenesis imperfecta can occur as an isolated clinical entity or as part of a syndromal diagnosis, examples include tricho-dento-osseous syndrome (MIM #190320), Jalili syndrome (MIM#217080), Heimler syndrome (MIM #234580) and enamel-renal syndrome (MIM #204690).The aim of this paper is to further characterize the clinical features of non-lethal Raine syndrome and compare them to other syndromic forms of amelogenesis imperfecta.

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2. Patients and methods

2.1. Clinical report

The propositus (III-7) was an18 year old girl born to a Moroccan consanguineous family. The parents were first cousins.She had a brother (III-10) of 15 years with same phenotype. She had another affected brother (III-8) with the same facial appearance, who died at 7 months of age because of an episode of severe diarrhea with dehydration. There are eight clinically unaffected siblings.

II-7 was delivered at term with noovert newborn phenotype. She had normal psychomotor development, with no learning or developmental disability. She attends mainstream school. She did not have epilepsy. At clinical examination at 14 years, she had normal measurements, her height was 161 cm (50th centile), her weight was 48 kg (50th centile), and her head circumference was 54 cm (50th centile). She had midface hypoplasia, a narrow prominent forehead, hypertelorism, down-slanting palpebral fissures, right convergent strabismus, a depressed nasal bridge, short nose, anteverted nostrils, long philtrum, high arched palate, gingivitis, prognathism, and low-set posteriorly rotated ears (Fig. 1). She had mesomelic short limbs, brachydactyly, broad thumbs, bulbous fingertips, clinodactyly of the fifth finger, and broad halluces with flat feet (Fig. 6).

The dental examination revealed thin, yellow and translucent enamel of uniform contour consistent with a diagnosis of hypoplastic amelogenesis imperfecta, type 4 according to Witkop classification (Witkop, 1988). A series of alternating vertical ridges and grooves affecting the maxillary and mandibular teeth was noted. Tooth decay was present in all teeth. Orthopantomograms revealed retention of the upper left canines (Fig. 2).The pulp chambers and roots appeared normal.

The auditory evoked potentials showed moderate hearing loss in the left (30 dB) and right (40 dB) ears.The karyotype was normal.A brain computerized tomography (CT) scan revealed intracranial calcifications in the white matter and globus pallidum. Renal ultrasonography revealed mild nephrocalcinosis in the renal medullae. Radiographs of the limbs demonstrated short distal phalanges, mild bowing of the radius and normal femurs (Fig. 3). There was no evidence of osteosclerosis in any of the investigated bones.

The biochemical analyses of III-7at 17 years of age showed normal serum calcium, and alkaline phosphatase and normal urinary calcium and phosphate. A mildly decreased serum phosphate of 2.2 mg/dL (normal range: 2.5–4.5 mg/dL) and elevated parathyroid hormone (PTH) level of 95.3 pg/mL (15–68 pg/mL) was detected.

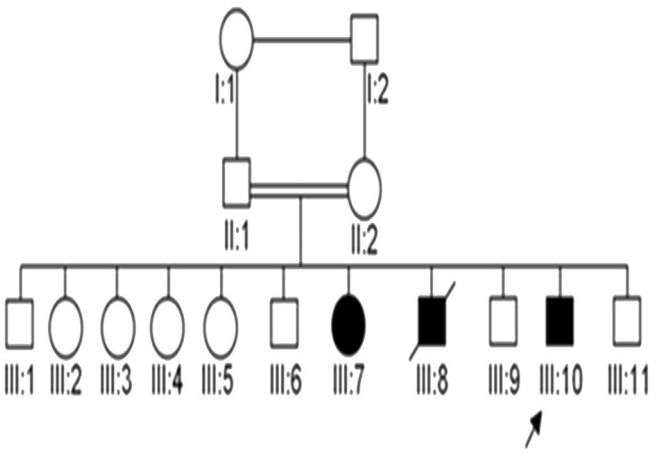

Fig. 1. Pedigree of the family.

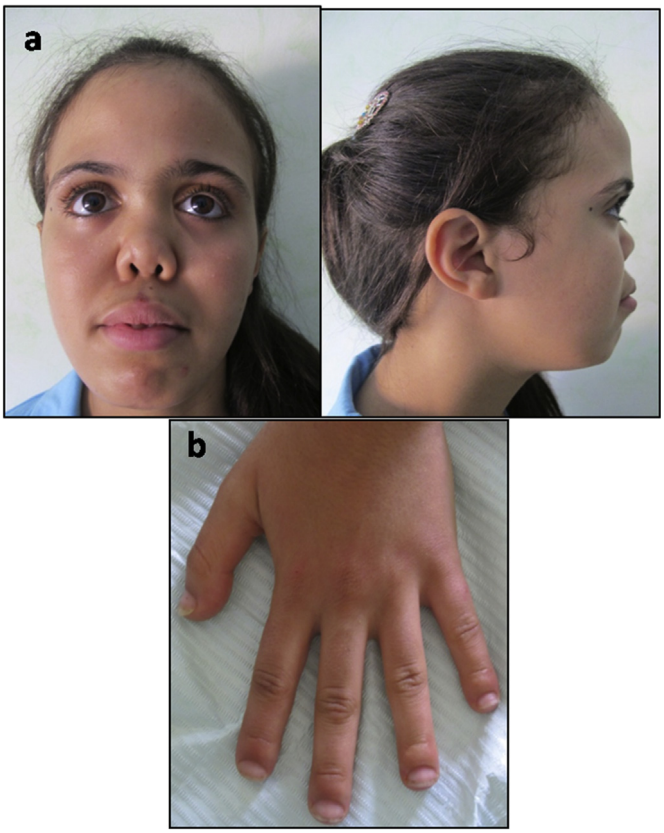

Fig. 2. (A) Facial photograph of the propositus showing the facial features of midface hypoplasia, a narrow prominent forehead, hypertelorism, down-slanting palpebral fissures, anda depressed nasal bridge, short nose, anteverted nostrils with long philtrum. (B) Photo of the hand of the propositus showing brachydactyly.

Her affected brother (III-10) was an 11 years old boy referred because of unusual facial features and amelogenesis imperfecta. He was delivered at term, but a complicated delivery resulted in cerebral hypoxia. Despite this he had normal initial psychomotor development, but currently has some minor speech problems and moderate learning disability. He had two epileptic episodes associated with fever at 3 years and 5 years. He was then monitored for epilepsy, and treated with sodium valproate. On clinical examination at 11 years, he had normal measurements, his length was 143 cm (50th centile), his weight was 34 kg (50th centile), and his head circumference was 52 cm (50th centile).He had the same facial features as his affected sister, but with a protruding tongue and more noticeable prognathism that affects his speech (Fig. 4). He also had broad thumbs and broad halluces with flat feet. He has some hearing impairment with auditory evoked potentials revealing moderate hearing loss in the left (60 dB) and right (40 dB) ears.

He has very poor oral hygiene, with abundant dental plaque and dental caries.The dental examination revealed hypoplastic amelogenesis imperfect in all teeth. The crowns of all the teeth appeared blanched, snow-capped, yellowish-brown, pitted, or grooved in shape. The enamel was thin on most of the areas and almost absent on the occlusal surfaces due to attrition. Significant gingivitis was observed on examination of the soft tissue (Fig. 5). Orthopantomograms showed thin enamel of all teeth and retention of both upper canines.The pulp chambers and roots appeared normal, and some teeth were absent (Fig. 4).The karyotype was normal. Both

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