European Journal of Medical Genetics 57 (2014) 536–542

Contents lists available at ScienceDirect

European Journal of Medical Genetics

journal homepage: http://www.elsevier.com/locate/ejmg

Review

Raine syndrome: An overview

Víctor Faundes [a,*], Silvia Castillo-Taucher [b,c], Patricio Gonzalez-Hormazabal [d], Kate Chandler [e], Andrew Crosby [f], Barry Chioza [f]

[a] Laboratorio de Genética y Enfermedades Metabólicas, INTA, Universidad de Chile, Santiago, Chile
[b] Sección Genética, Departamento de Medicina, Hospital Clínico Universidad de Chile, Santiago, Chile
[c] Laboratorio de Citogenética, Clínica Alemana, Santiago, Chile
[d] Laboratorio de Genética Molecular Humana, Programa de Genética Humana, Instituto de Ciencias Biomédicas, Universidad de Chile, Santiago, Chile
[e] Manchester Centre for Genomic Medicine, Central Manchester University Hospitals NHS Foundation Trust, Manchester, United Kingdom
[f] Monogenic Molecular Genetics, University of Exeter Medical School, St. Luke's Campus, Exeter, United Kingdom

ARTICLE INFO

Article history:
Received 12 March 2014
Accepted 3 July 2014
Available online 12 July 2014

Keywords:
Skeletal dysplasia
Osteosclerosis
FAM20C
Respiratory distress

ABSTRACT

Raine syndrome (RS) is a bone dysplasia characterised by generalised osteosclerosis with periosteal bone formation, characteristic face, and brain abnormalities [MIM # 259775]. Its prevalence is estimated to be < 1/1,000,000. Although it was originally thought always to be lethal, there have now been six reports of patients surviving into childhood and this phenotype is still being defined. The skeletal dysplasia predominantly affects craniofacial development explaining the severe proptosis, underdeveloped midface, depressed nasal bridge and short nose. The main radiological manifestation is a diffuse, marked osteosclerosis of the base of skull and long bones. Raine syndrome is caused by biallelic mutations in *FAM20C*, located on chromosome 7p22.3. This gene encodes a Golgi casein kinase, which phosphorylates serine residues of extracellular proteins involved in biomineralisation. Facial appearance and radiological findings allow the clinical diagnosis, and molecular testing of *FAM20C* can confirm this. Desmosterolosis and congenital cytomegalovirus infection may resemble Raine syndrome. If Raine syndrome is suspected prenatally the newborn should be admitted at a neonatal intensive care unit as significant respiratory distress is often present immediately after birth.

We present here a review of the pertinent literature in clinical manifestations, molecular background, diagnosis and management.

1. Introduction

Raine syndrome has been defined as a syndrome characterised by generalised osteosclerosis, characteristic face, brain abnormalities including intracerebral calcifications, and neonatal lethality [Hennekam, 2008]. Six cases that survived into childhood and who showed abnormal psychomotor development, have been reported and one may wonder whether the adjective "lethal" should still be used [Fradin et al., 2011; Hennekam, 2008; Rafaelsen et al., 2013; Simpson et al., 2009]. Raine syndrome (RS; ORPHA1832; MIM 259775) has been classified in Group 22 of genetic skeletal disorders, the neonatal osteosclerotic dysplasias [Warman et al., 2011].

2. Epidemiology

To date, thirty-five cases have been described, and its prevalence is estimated to be < 1/1,000,000 [Hennekam, 2008]. As its clinical phenotype postnatally is not yet defined well RS should be considered in undiagnosed infants or children with facial or radiological characteristics showing some resemblance to RS. RS was initially described in a Caucasian patient but most reported cases have been of Arab ancestry and some from Brazil, Sudan and India. Indeed, RS is globally occurring although its occurrence may be increased in inbred populations (Table 1).

3. Clinical description

The first reported case was a female newborn, who presented microcephaly, wide fontanelles, prominent exophthalmos, depressed nasal bridge, choanal atresia, underdeveloped midface hypoplasia, low-set ears, micrognathia, tented upper lip, cleft soft

* Corresponding author. Laboratorio de Genética y Enfermedades Metabólicas, Instituto de Nutrición y Tecnología de los Alimentos (INTA), Universidad de Chile, Av. El Líbano 5524, P.O. 7830490, Santiago, Chile. Tel.: +56 229781478.
E-mail address: vfaundes@inta.cl (V. Faundes).

http://dx.doi.org/10.1016/j.ejmg.2014.07.001
1769-7212/

Table 1
Demography and reproduction in reported individuals with Raine syndrome.

Antecedent	Frequency [n (%)][a]	Reference
Demographic		
- Ethnicity		
• Arab	23 (65.7)	Ababneh et al. [2013]; Al-Gazali et al. [2003]; Al Mane et al. [1996, 1998]; Fradin et al. [2011]; Gaigi et al. [2011]; Güneş et al. [2005], Hülskamp et al. [2003]; Koob et al. [2011]; Mahafza et al. [2001]; Patel et al. [1992]; Rejjal [1998]; Rickert et al. [2002]; Simpson et al. [2007]
• Caucasian	5 (14.3)	Kan and Kozlowski [1992]; Kingston et al. [1991]; Rafaelsen et al. [2013]; Raine et al. [1989]
• Brazilian	1 (2.8)	Acosta et al. [2000]
• Indian	1 (2.8)	Kochar et al. [2010]
• African	1 (2.8)	Michael et al. [2011]
• Mixed	1 (2.8)	Chitayat et al. [2007]
• Not reported	3 (5.7)	Shalev et al. [1999]; Simpson et al. [2009]
Reproduction		
- Consanguinity	15 (42.3)	Ababneh et al. [2013]; Acosta et al. [2000]; Al Mane et al. [1996, 1998]; Fradin et al. [2011]; Gaigi et al. [2011]; Güneş et al. [2005]; Kingston et al. [1991]; Kochar et al. [2010]; Koob et al. [2011]; Mahafza et al. [2001]; Michael et al. [2011]; Rickert et al. [2002]; Shalev et al. [1999]; Simpson et al. [2007], [2009]
- Previous miscarriage/stillbirth	3 (8.6)	Michael et al. [2011]; Raine et al. [1989]; Rickert et al. [2002]
- Family history of malformations	2 (5.7)	Acosta et al. [2000]; Al Mane et al. [1996]
- Previous child with Raine syndrome	6 (17.1)	Al Mane et al. [1996]; Gaigi et al. [2011]; Mahafza et al. [2001]; Rafaelsen et al. [2013]; Rejjal [1998]; Rickert et al. [2002]
- Infections/drugs in pregnancy	1 (2.9)	Güneş et al. [2005]

[a] Percentage calculated from a total of 35 cases officially reported.

palate, and hyperplastic gums [Raine et al., 1989]. Subsequently several other characteristics have been described, but the original findings remain the most characteristic (Fig. 1.; Table 2). There is no significant difference in signs and symptoms between genders. Almost all spontaneous deliveries are born at term, and newborns are small for gestational age and have respiratory distress. The skeletal dysplasia affects craniofacial development more than spine and the limbs, which is evident in the proptosis, underdeveloped midface, and depressed nasal bridge and short nose, all key indicators for the diagnosis. Occasionally findings are optic atrophy, mild right ventricle enlargement, patent ductus arteriosus and foramen ovale [Shalev et al., 1999], deep dorsal skin wrinkles over fingers and toes [Mahafza et al., 2001], microscrotum [Hülskamp et al., 2003] and hypotonia [Ababneh et al., 2013; Rafaelsen et al., 2013].

The physical manifestations observed in non-lethal cases are similar to those described in lethal cases, albeit that craniofacial signs are attenuated throughout life. Development and growth vary considerably. Three patients had a delayed psychomotor development and three others followed a normal development; three had short stature and three had normal growth parameters. However, there is no correlation between psychomotor development and growth parameters. Other manifestations in non-lethal RS include hydrocephalus, seizures, dysphagia, pectus excavatum, hearing loss, visual impairment, pyriform aperture stenosis, dental anomalies, and hypophosphataemia [Fradin et al., 2011; Rafaelsen et al., 2013; Simpson et al., 2009].

4. Aetiology

Simpson et al. (2007) identified four non-synonymous base changes and four splice-site changes in *FAM20C*, a 10-exon gene that represents the most telomeric confirmed gene on chromosome 7p22.3, and to date, is the only disease-causing gene for RS. *FAM20C* was initially discovered in murine cell lines during in vitro hematopoiesis, and forms part of "Family with sequence similarity 20", which encompasses three members [Nalbant et al., 2005]. This family is evolutionarily conserved in mammalians and invertebrates [Nalbant et al., 2005]. The proteins that comprise this group possess two domains: an N-terminal signal sequence (SS) and the conserved C-terminal domain (CCD) [Nalbant et al., 2005]. CCD is the most conserved region through the

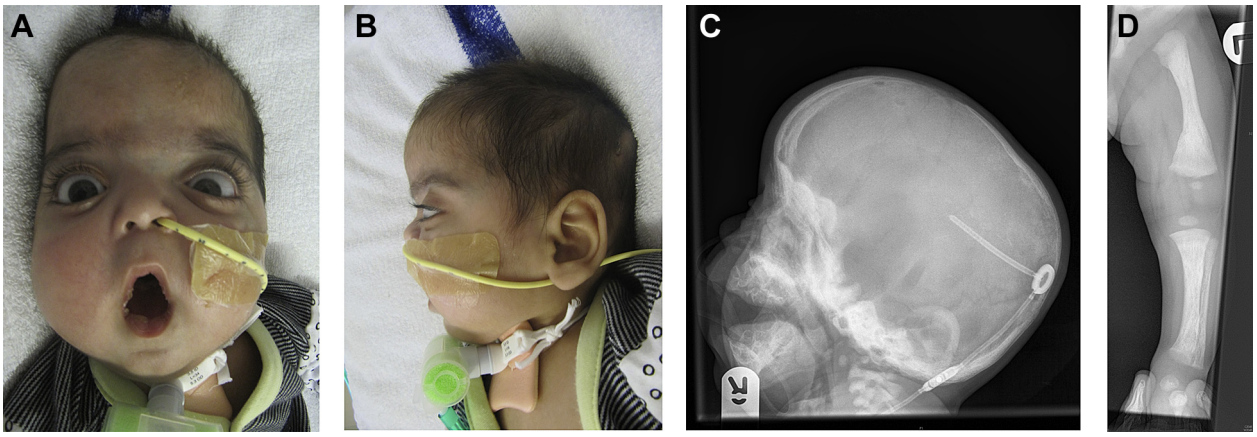

Fig. 1. Clinical and radiological manifestations of Raine syndrome. Frontal (A) and lateral (B) view of a patient. Note the marked exophthalmos, depressed nasal bridge, underdeveloped midface, micrognathia and tented upper lip. The skull radiograph (C) shows a marked sclerosis of the base of skull and facial bones, whereas the limb radiograph (D) evidences a poor corticomedullary demarcation of long bones as well as a broad femoral neck.