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Genetics

Carpenter Syndrome: Report of Two Cases

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Abstract | **Case Report**

Carpenter syndrome (MIM 201000) is a rare autosomal recessive disorder characterized by combination of acrocephaly, syndactyly and brachydactyly in the hands as well as syndactyly and preaxial polydactyly of the toes. Other variable features can be present. 100 patients have been reported until now, with 14 mutations in the conserved sequence encoding the ras-like in rat brain 23 (*RAB23*) gen identified. We report here two Moroccan cases with a typical clinical picture of carpenter syndrome.

Keywords: Case report, Carpenter syndrome, rare disorder, *RAB23*.

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BACKGROUND

Carpenter syndrome (CS) comprises varying degrees of craniosynostosis, brachydactyly and syndactyly of hands and feet, polysyndactyly of the great toes, congenital heart defects, bone abnormalities, short stature, and obesity. This syndrome caused by biallelic mutations in the *RAB23* gene which acts as an essential negative regulator of the Sonic hedgehog signaling pathway.

CASE PRESENTATION

Cas 1

A 2 months old male baby born to consanguineous parents (first degree), was referred to our medical genetic consultation for polymalformatif syndrome. The pregnancy was medically followed, and it was without reported complications. The mother had no history of drug ingestion, radiographic examination, or abdominal trauma during pregnancy. There was no family history of congenital anomalies. The infant was the second liveborn to a 24-year-old mother and 32-year-oldfather. On evaluation both the parents and the older sister were found to be normal. On a general physical examination, the patient had normal measurements. He was dysmophic with a brachycephaly, a hypotelorism with upslanting palpebral fissures, bilateral epicanthus, wide nasal bridge and tip, a long philtrum, micrognathic mandible and a low set ears. The intra-oral examination was normal at this age.

The boy also had brachydactyly with contractures of the proximal interphalangeal joints, polydactyly postaxial in the hands. There was preaxial polydactyly of both feet and syndactyly of all the other toes. There was bilateral metatarsus varus.

Cranial CT scan confirmed the presence of a complex synostosis of all sutures (oxycephaly), with a Partial hypoplasia of the corpus callosum. Cardiac ultrasonography revealed pulmonary stenosis with Abnormal venous return and the abdomino-renal ultrasonography confirmed the ombilical hernia with a normal kidney. The results of all laboratory examinations were within normal limits, and a chromosomal investigation revealed a normal boy karyotype, 46 XY. Ophthalmological examination was normal. At the age of 3 mouths we don't have a idea of the intellectual development.

Case 2

A 6 months old male baby born, no consanguineous, was hospitalized in the neurosurgery department for management of craniosynostosis complicated with a intracranial hypertension. The pregnancy was medically followed, and it was without reported complications. There was no family history of congenital anomalies.

The clinical examination of the patient revealed clover leaf deformity with ptosis of the cerebral parenchyma at the anterior fontanel. A hypotelorism with upslanting palpebral fissures, bilateral epicanthus was also present in this patient with collateral venous circulation at the forehead. In these limbs, he had a partial membranous syndactyly in the index and the middle finger in the right hand, short fingers and anomalies in the implantation of the toes.

Cranial CT scan confirmed the presence of a complex synostosis of all sutures (oxycephaly), with a Ptosis of the parenchyma at anterieor fontanel. Cardiac ultrasonography revealed interventricular communication ans the abdomino-renal ultrasonography was normal.

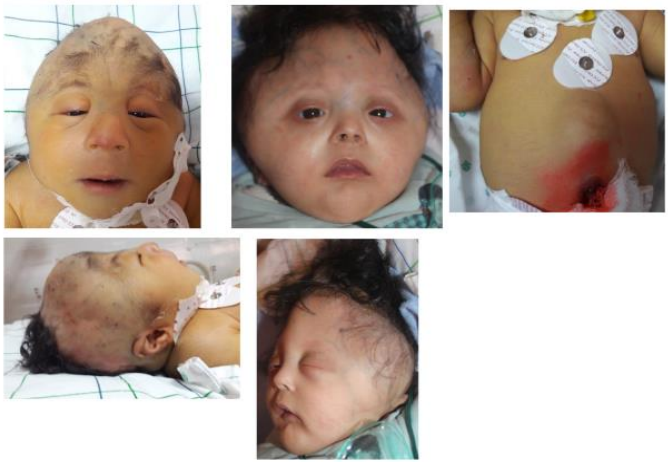

Figure 1: Pictures of the patients showing the dysmorphic face and ombilical hernia

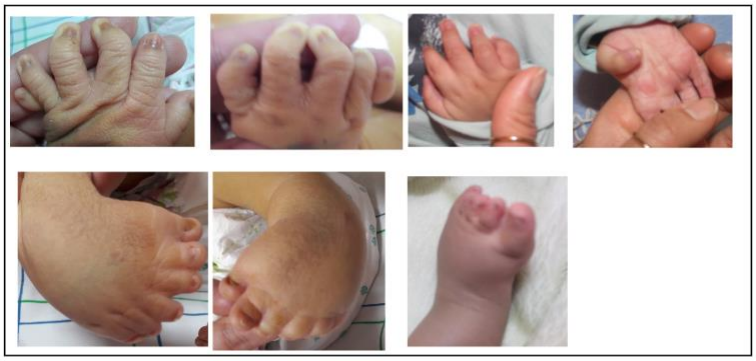

Figure 2: Hand and foot abnormalities in both patients

Table 1: Mutations reported in patients with Carpenter syndrome

	Exons	DNA	Protein	References
Missense and Nonsense mutations	Exon 1	c.35T>A	p.Met12Lys	Jenkins et al. , 2011
	Exon 1	c.82G>A	p.Arg28Gln	Fujikura (2016) PLoS One 11, e0155552
	Exon 3	c.253 T>C	p.Cys85Arg	Jenkins et al. ,2007
	Exon 4	c.434T>A	p.Leu145Ter	Jenkins et al. ,2011
	Exon 1	c.82C>T	p.Arg28Ter	Jenkins et al. ,2011
Splicing mutations		c.156-3T>G	p.Val53fster13	Jenkins et al. ,2011
		c.482-1G>A	p.Val161fster3	Ben-Salem et al. ,2013
		c.482-1G>C	p.Val161Leufs*16	Haye et al. 2014
Small deletions	Exon 2	c.234_236delCTA	p.Tyr79del	Jenkins et al. ,2011
	Exon 2	c.232delT	p.Tyr78fsTer30	Jenkins et al. ,2007
Small insertions	Exon 1	c.86dupA	p.Tyr29Ter	Alessandri et al. ,2010
	Exon 1	c.140_141insA	p.Glu48fsTer7	Jenkins et al. ,2007
	Exon 4	c.408_409insT	p.Glu137Ter	Jenkins et al. ,2007
	Exon 3	c.362_363insG	p.Asn121fsTer4	Jenkins et al. ,2011

DISCUSSION

The description of the clinical spectrum of CS was gradual over decades. It was first described in 1901 by George Carpenter and later classified as one of the acrocephalopolysyndactyly syndromes [2]. CS (MIM 201000) is a rare autosomal recessive disorder characterized by combination of acrocephaly, syndactyly and brachydactyly in the hands as well as syndactyly and preaxial polydactyly of the toes. Other variable features include mental retardation, obesity, and hypogonadism [2-4, 15]. Around 100 patients have been described [10].

The clinical picture includes multiple suture (sagittal, lambdoid and coronal) Craniosynostosis, a dysmorphic face with limbs abnormalities: bifid or broad thumbs, small or absent middle phalanges, cutaneous syndactylies, post-axial polysyndactyly of the hands, and preaxial polydactyly of feet [2-5].

Associated to this clinical symptoms, other manifestations include congenital heart defect, increased birth weight, later obesity, cryptorchidism or hypoplastic testes, umbilical hernia, talipes, bowed femora and tibiae, central nervous system malformations, and intellectual disability can be present, Altunhan *et al*., 2011).

Cases of CS have been described throughout the world, ranging from Europe and America to case reports described in the Indian and the Middle East. Our patients are the first African patients confirmed with a CS. The clinical and radiological features of the patient s were typical to CS. Facial anomalies are similar to those described in patients with CS. The abnormalities in the hands and feet are typical to CS [3-5]. The radiological investigations have reinforced the diagnosis of CS in our patients.

Using homozygosity mapping, Jenkins et al. identified the gene of this syndrome, is loctated at chromosome 6p12.1-q12 and simultaneously reported five gene mutations [1]. The *RAB23* gene comprises one noncoding and six coding exons, with an interval region of 35.43 kb, belongs to the RAB family of 160 small guanosine triphosphatases (GTPases), encodes a small GTPase of the Ras superfamily which acts as an essential negative regulator of the Sonic hedgehog signaling pathway [1, 6, 7].

The nonsense mutation and loss of protein of Rab23 has been associated with neural tube defect in mice and aberrant expression in various diseases in human such as neural system, breast, visceral, and cutaneous tumor. In addition, Rab23 may play joint roles in autophagosome formation during anti-infection process against Group A streptococcus [8].

To date, 14 mutations including eleven truncating (two nonsense, six insertion/deletion, three splice site mutations) and three missense have been reported in patients with CS syndrome with a recurrent mutation (p.Leu145Ter) indicating a founder effect in patients of north European origin [1, 9, 14, 10-13].

CONCLUSION

We report though this work the first Moroccan series with a typical symptoms of Carpenter syndrome demonstrates the importance of a genetic consultation in the diagnostic of the rare diseases.

Abbreviations

CS: Carpenter syndrome
RAB23: RAS-ASSOCIATED PROTEIN

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