International Journal of Medicine and Medical Sciences Vol. 4(3), pp. 60-64, March 2012
Available online http://www.academicjournals.org/IJMMS
DOI: 10.5897/IJMMS12.029
ISSN 2006-9723 ©2012 Academic Journals

Full Length Research Paper

A new craniosynostosis syndrome

Cyrus Azimi

Genetics Group, Cancer Research Center, Cancer Institute of Iran, Tehran University of Medical Sciences, Tehran, Iran.
E-mail: azimicyrus@tums.ac.ir or cazimi3000@yahoo.com.

Accepted 23 December, 2011

We report on a patient with bilateral multiple craniosynostosis involving the coronal and lambdoid sutures, high myopia, obesity, vertebral anomalies, minor acral anomalies and normal intelligence. The clinical features are not typical of any known craniosynostosis syndrome. Search of POSSUM, London Dysmorphology Database (LDDB), online Mendelian Inheritance in Man (OMIM), and the medical literature failed to find any similar case. The constellation of manifestations in this patient suggests a previously unrecognized syndrome resembling Carpenter syndrome.

Key words: New syndrome, craniosynostosis, Carpenter syndrome.

INTRODUCTION

Craniosynostosis (premature suture fusion) can be either classified as simple or multiple. In simple craniosynostosis, only one suture is involved. In multiple craniosynostosis, two or more sutures are synostosed. Multiple synostosis occurs in approximately 5% of nonsyndromic cases of craniosynostosis (Cohen and MacLean, 2000). Two-suture synostosis accounts for about two-thirds of the cases, while more than two sutures are involved in one-third of the cases. The more sutures synostosed, the greater the risk for an individual to bear mental retardation. About 35% of cases with more than two sutures synostosed show lacunae (small cavities within the bone matrix containing osteocytes) in their skull radiographies (Cohen and MacLean, 2000).

A number of craniofacial syndromes with multiple suture synostosis have considerable overlap in their manifestations. Bilateral coronal synostosis is the most commonly observed, however bilateral coronal and lambdoid synostosis or a combination of bilateral coronal synostosis and sagittal synostosis have also been noted, amongst other combinations (Barkovich, 2000). When the sagittal suture is synostotic in conjunction with both coronal sutures (and, sometimes, both lambdoid sutures), the membranous bone of the calvaria expands between the sutures, resulting in a characteristic lobulated skull configuration known as cloverleaf skull [Kleeblattschadel] (Angle et al., 1967; Lodge et al., 1993; Cohen, 1993; Goh et al., 1997). Carpenter syndrome, although it was first described in 1901and 1909 by George Carpenter (British physician), it was not recognized as a distinct nosologic and genetic entity, and as a new syndrome (acrocephalopolysyndactyly type II) until Samia Temtamy's article (Egyptian physician) in 1966. Sakati et al. (1971) have suggested that this syndrome might more appropriately be called the Temtamy syndrome, as the sisters originally reported by Carpenter did have cranial sutures and had other differences from Temtamy's patient and others reported since. About 100 cases have been described in the worldwide medical literature, therefore, Carpenter syndrome is one of the rarest forms of the craniofacial disorders and has an estimated occurrence rate of approximately one in a million male and female live births. In addition to the multiple suture craniosynostosis, which may present as a cloverleaf skull, the most characteristic abnormality of the Carpenter syndrome is the presence of polydactyly of the fingers and or toes; brachydactyly and syndactyly of the hands (Saxena et al., 1970; Cohen, 1979; Goodman et al., 1979).

Other abnormalities include congenital heart defects, obesity, short stature and mental retardation (Robinson et al., 1985; Cohen and MacLean, 2000), and also bilateral sensorineural hearing loss (Tarhan et al., 2004). Mild to moderate mental deficiencies are common (about 75% of all cases) and IQ score have ranged from 52 to 104 (Frias et al., 1978; White et al., 1987; Jamil et al., 1992; Richieri-Costa et al., 1993).

Autosomal recessive inheritance is supported by the reports of families with consanguinity (Der Kaloustian et al., 1972; Richieri-Costa et al., 1993) and multiple

affected siblings (Carpenter, 1901; Frias et al., 1978; Cohen et al., 1987). Sporadic cases have also been reported by some authors (Sunderhaus and Wolter, 1968; Eaton et al., 1974; Cohen, 1975). Most of the affected patients have a surgical procedure between 3 and 9 months of age to open the cranial vault to make space for the brain to grow (McCarthy et al., 1978). Hidestrand et al. (2009) reported an adult patient with Carpenter syndrome who was unusual in that she has never had surgical intervention.

MATERIALS AND METHODS

We report on a patient with manifestations resembling Carpenter syndrome including multiple suture craniosynostosis, obesity, short stature and syndactyly of the feet. She was born in 1990, and was referred to our department for diagnosis and further investigations at birth, by her pediatrician. We followed up her health condition for 15 years until she left and immigrated to other country.

RESULTS

Clinical report

The proposita presented with craniosynostosis and multiple congenital anomalies was the second child born to a non-consanguineous Ashkenazi Jewish couple. The parents were both 33 years old at the time of birth and phenotypically normal. They had an older healthy daughter. The family history was negative for craniosynostosis.

Pregnancy history was unremarkable. The delivery was at 37 weeks of gestation by Cesarean section. Her birth weight was 2296 g (<3rd centile), OFC was 28.5 cm (<2nd centile) and length was 48.2 cm (20th centile). The abnormal head shape was noted at birth, along with a single umbilical artery. Physical exam at the age of 12 days showed an alert, small and active baby with an elongated head and large anterior fontanel (5×7 cm). She had an apparent hypertelorism, with short palpebral fissures, and shallow orbits. There was a flat nasal bridge with upturned nasal tip. She had a long philtrum. Her ears, oral cavity, chin and neck were unremarkable.

Head CT scan confirmed premature bilateral synostosis of the coronal and lambdoid sutures. The remaining sutures appeared to be patent. However, the base of the skull appeared quite short and there was some parietal bossing consistent with a Kleeblattschadel (cloverleaf skull). Bony dysplasia was present in the parietal occipital region. The calvarium did not appear to be enlarged. Hypertelorism was also noted on the skull X-ray, but did not show any lacunae. Renal ultrasound was normal.

The patient had several surgeries at the age of 2 weeks, 11 months and 2.5 years for suture release and cranial vault reshaping. In addition, she had tonsillectomy and adenoidectomy at 6 and 7 years of age. Her physical and mental development has been normal and she was studied at the public school.

At the age of 10 years, examination showed her head circumference was 50.5 cm (20th centile), her height was 147.5 cm (95th centile) and her weight was 42.5 kg (95th centile). Her head appeared to be large with turricephalic shape with some bitemporal and biparietal narrowing and mild supra-auricular bossing. She had a round face with mild bilateral ptosis and slight antimongoloid slant of palpebral fissures. Her inner canthal distance was 3 cm and outer canthal distance was 9 cm. Her thumbs were relatively slender and there was mild fifth finger clinodactyly. Her feet were well formed.

At the age of 15 years, on examination, she was a very cooperative girl who had thick glasses for myopia and appeared obese. Her OFC was 51 cm (<2nd centile), height 151 cm (3rd centile) and weight 70.2 kg (95th centile). She had a high forehead with bitemporal narrowing and round face. She had shallow orbits with slightly prominent eyes, bilateral upper lid ptosis and recession of the lateral portion of the orbits. She had a narrow palate, retrognathia, and dental malocclusion (wears orthodontic brace). Her feet were small and had partial second and third toe syndactyly. Skin examination was normal with no evidence of acanthosis nigricans. Examination of cardiac, uro-genital and other organs was unremarkable.

Three-dimentional CT scan of the brain showed mild brachycephaly with turricephaly, but bilateral symmetry through the cranium, skull base and maxillo-facial skeleton, except for mild flattening of the right parieto-occipital region. Facial slope was flat in the mid-orbital and mid-maxillary regions, with bilateral mild to moderate proptosis.

Skeletal survey showed changes in the skull consistent with prior craniosynostosis repair, calcification of the anterior longitudinal ligament in the cervical spine with minor changes of bone formation, and elongated vertebral body height, most evident in the lumbar spine. Asymmetric spinal dysraphism in lower lumbar/upper sacral segments, and mild bilateral hallux valgus were also noticed. Orthopedic examination and the X-ray of the flexion/extension views of the neck showed that there were some congenital abnormalities of the vertebral bodies with some anterior osteophytes, but she seemed to have a good range of motion of her neck and was stable.

Ophthalmological examination showed severe myopia of -14 Diopters. Her chromosomal study was normal.

Mutation analysis for *FGFR1* (P252R), *FGFR2* (exons IIIa and IIIc), *FGFR3* (P250R), and *TWIST* (entire coding region) genes revealed no mutations (O'Rourke et al., 2002; Morriss-Kay and Wilkie, 2005).

Differentiation of clinical features of Carpenter syndrome and our patient are shown, in most details, in Table 1. Unfortunately, our patient and her parents were not consented to take photographs of her.

Table 1. Differentiating characteristics of Carpenter syndrome and presented patient.

Manifestation	Carpenter syndrome	Presented patient
Craniosynostosis sutural involvement	Sagittal, bilateral coronal and lambdoid	Bilateral coronal and lambdoid
Acrocephaly/turricephaly	+	+
Brachycephaly	+	+
Clover leaf skull	+	+
Short neck	+	-
Sloping/high forehead	+	+
Flat nasal bridge	+	+
Upturned nasal tip/anteverted nostils	+	+
Hypertelorism	+	+
Shallow orbits	+	+
Bilateral ptosis	+	+
Epicanthic folds	+	+
Sclerocornea/microcornea/optic atrophy	+	-
High myopia	-	+
Midfacial hypoplasia (flat facial profile)	+	-
Micrognathia/retrognathia	+	+
High-arched/narrow palate	+	+
Dysplastic ears	+	-
Low-set ears	+	-
Single flexion crease of the hands	+	-
Polydactyly of the hands	+	-
Partial syndactyly and camptodactyly of the hands	+	-
Brachydactyly of the hands	+	-
Clinodactyly of the hands	+	+
Preaxial polydactyly of the feet	+	-
Partial syndactyly of the feet	+	+
Hypoplasia/aplasia of the middle phalanges of fingers and toes	+	-
Subluxation at distal interphalangeal joints	+	-
Angulation deformities at knees	+	-
Umbilical hernia	+	-
Omphalocele	+	-
Postnatal growth less than 25th centile	+	+
Short stature	+	+
Acral anomalies	+	+
Obesity	+	+
Genital abnormalities/hypogenitalism	+	-
Mental deficiency/developmental delay	Common	-
Congenital heart defects (ASD, VSD, PDA, PS, TF, TGV)	Common	-
Genu valgum	Common	-
Lateral displacement of patellae	Common	-
Vertebral anomalies	Occasional	+
Proptosis	Occasional	+
Lacunae (in skull x-ray)	Occasional	-
Marked cranial asymmetry	Occasional	-
Slight downslanting palpebral fissures	Occasional	+
Dental problems (partial anodontia/malocclusion)	Occasional	+
Hearing loss (conductive and neurosensory)	Occasional	-
Duplication of second phalanx of thumbs	Occasional	-
Hallux valgus	Occasional	+
Coxa valga	Occasional	-

Table 1. Contd.

Metatarsus varus	Occasional	-
Flare to pelvis	Occasional	-
Flat acetabulum	Occasional	-
Absent coccyx	Occasional	-
Spina bifida occulta	Occasional	-
Scoliosis	Occasional	-
Pilonidal dimple	Occasional	-
Hydronephrosis with/without hydroureter	Occasional	-
Accessory spleen	Occasional	-
Precocious puberty	Occasional	-
Inheritance	AR	AR

AR, Autosomal recessive. ASD, atrial septal defect; VSD, ventricular septal defect; PDA, patent ductus arteriosus; PS, pulmonary stenosis; TF, tetralogy of Fallot; TGV, transposition of the great vessels.

DISCUSSION

Multiple craniosynostosis including coronal and lambdoid sutures is present in a vast range of syndromes (Cohen and MacLean, 2000).

The constellation of anomalies in our patient is dissimilar to those previously reported. However our patient does resemble Carpenter syndrome, particularly with regard to the craniosynostosis, which appeared to cause a Kleeblattschadel anomaly, syndactyly of the feet, short stature and obesity. The differences, however allow nosologic splitting.

A few authors observed Carpenter syndrome among siblings (Gershoni-Baruch, 1990; Islek et al., 1998). Perlyn and Marsh (2008) reported a retrospective review on three siblings, all affected with Carpenter syndrome. They concluded that the diverse anatomical variation seen in these three siblings supports the notion of marked phenotypic variability within this syndrome. Therefore, our patient may represent an extension of the Carpenter syndrome phenotypic or more probable a new craniofacial syndrome. Further research will help resolve this and similar case reports, in the medical literature.

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