Case Reports

Apert syndrome in a Sri Lankan boy with normal head growth and without clinical features of raised intracranial pressure during infancy

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Introduction

Apert syndrome is a rare syndrome with autosomal dominant inheritance affecting 1 in 65,000 newborns[1,2]. It is a type of acrocephalosyndactyly characterized by craniosynostosis, midfacial hypoplasia and symmetrical syndactyly[1]. The first case was reported in 1842 by Baumgartner and the next in 1894 by Wheaton[3]. However, the syndrome was finally named after the French paediatrician Eugene Apert who published a case series in 1906[3,4]. Apert syndrome is known for craniosynostosis which invariably manifests in the first year of life and accounts for 4% of all cases of craniosynostosis[4]. Babies with Apert syndrome usually develop craniosynostosis in early infancy and require craniectomy at the age of 6 months to one year[3,4]. We report a baby with Apert syndrome with normal head growth without any clinical signs of raised intracranial pressure (ICP) during the first year of life.

Case report

A baby boy was born as the second child to non-consanguineous, apparently healthy Sri Lankan parents at a Base Hospital. There was no family history of congenital malformations. The pregnancy was planned with pre-conceptional folic acid supplementation. The antenatal period was unremarkable with two ultrasound scans performed at two months and six months of gestation. The two antenatal scans did not pick up any abnormalities.

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The sibling of the patient was a healthy four-year-old boy who was thriving well and who achieved normal developmental milestones. Both parents were 35 years of age at the time of conception of the second pregnancy. At birth, the abnormal morphology of the newborn was noted which included an abnormal head shape (tall and anteroposterior diameter shortened), with a protuberant frontal region and flat occiput (Figure 1A, 1B**).** He had a partially fused coronal suture and agenesis of the sagittal and metopic sutures which resulted in a wide defect extending from the glabella to the posterior fontanelle. The following facial dysmorphic features were also observed: ocular proptosis, horizontal strabismus, hypertelorism with antimongoloid (downward slant of the lateral canthus and palpebral fissure) eyes (Figure 1C). He also had a flat nasal bridge and a thick nose with a bulbous tip. Both lips had a cross-bow appearance (Figure 1A, 1B, 1C).

Bilateral symmetrical syndactyly with fusion of four digits and both thumbs directed towards the palms was noted in the upper extremities (Figure 2A, 2B). Bilateral symmetrical syndactyly with deformed big toes was present in both lower limbs (Figure 2C, 2D).

Oral examination revealed a V shaped maxillary arch. The rest of the systems examination was normal. A clinical diagnosis of Apert syndrome was made and multidisciplinary care was offered. Genetic confirmation was attempted but financial constraints and the Covid-19 pandemic prevented us sending a sample to an overseas reference laboratory. His vision and hearing screening were normal. Echocardiogram revealed a small ostium secundum atrial septal defect with a left to right shunt. He was referred to a plastic surgical team to correct the syndactyly and to perform a craniectomy once craniosynostosis is established. The occipito-frontal circumference (OFC) was closely monitored monthly to detect the imminent craniosynostosis with raised ICP. Usually, craniectomy is performed from the age of 6 months onwards. However, in this baby the OFC has been increasing satisfactorily and at the age of 1 year it was lying in between the

median +1 standard deviation (Figure 3). There were no other clinical features suggestive of raised ICP. Surgery (cranioplasty with fronto-orbital advancement) was performed at the age of 16 months. Developmentally he could stand without support and had developed a mature pincer grasp by the age of 16 months. He could speak two to three words at this age and also could wave bye. The parents were counselled regarding the syndrome and its complications and the probability of genetic inheritance.

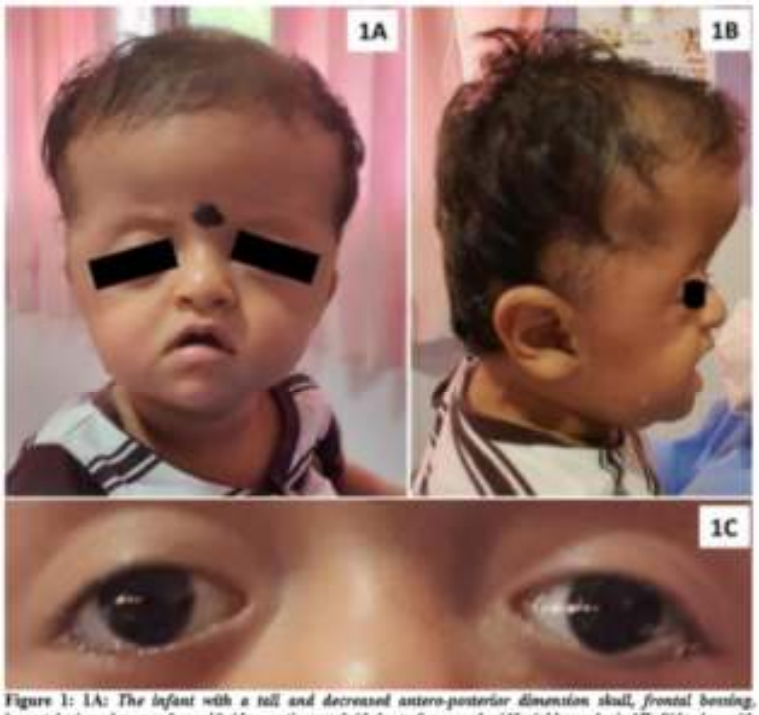

Figure 1: 1A: *The infant with a tall and decreased antero-posterior dimension skull, frontal bossing, hypertelorism, depressed nasal bridge, antimongoloid slant of eyes and midfacial hypoplasia 1B: Side view with prominent frontal bossing 1C: Hypertelorism, downward slant of lateral canthus and palpebral fissure*

**Permission given by parents to publish photograph*

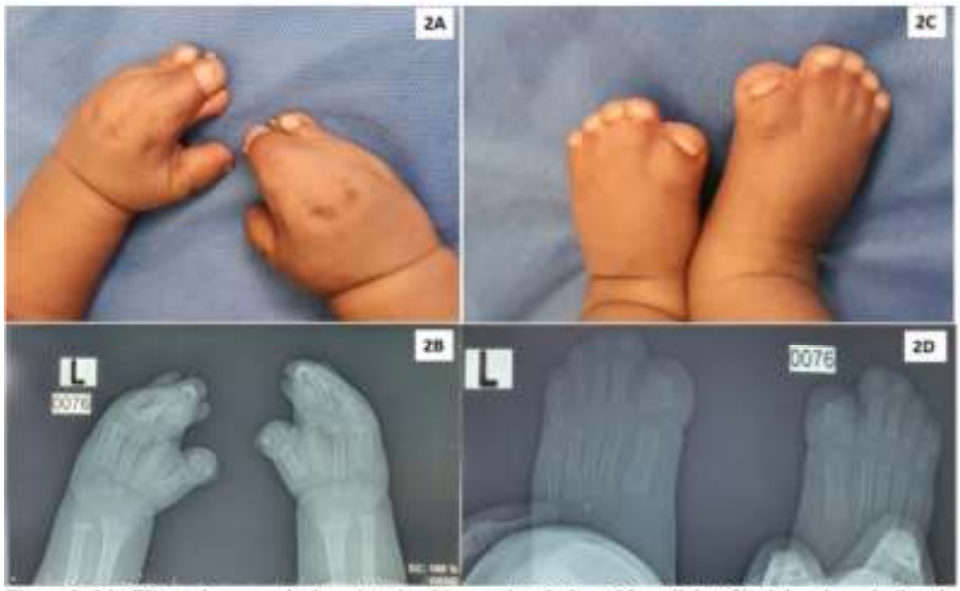

Figure 2: 2A: *Bilateral symmetrical syndactyly with complete fusion of four digits of both hands excluding the thumbs (both thumbs are directed towards the palm- inwardly placed) -2B: X-ray of both hands 2C: Bilateral symmetrical syndactyly of both feet with deformation of the big toes 2D: X-ray of both feet: Soft tissue fusion of all the digits with deformed big toes*

Figure 3: ***The OFC chart of the baby***

Discussion

Apert syndrome in 95% of cases occur as a sporadic mutation of fibroblast growth factor- receptor- 2 (FGFR2) gene on chromosome 10q25-q26 gene locus[1]. This passes across generations with autosomal dominant inheritance[3]. The mutation leads to altered signaling by FGFR2 which plays a key role during *in-utero* development in skeletal tissue formation[3]. This results in premature fusion of the skull and abnormal fusion of digits in hands and feet[5]. The typical turri-brachycephalic head shape is due to early craniosynostosis of coronal suture and agenesis of sagittal and metopic sutures[3, 6]. This will result in a wide defect extending from the glabella to the posterior fontanelle[6]. Premature closure of sutures with continued brain growth can lead to increased ICP which can be seen as copper beaten appearance on the skull x-ray[1,3]. Shortening of the bony orbit manifests as ocular proptosis, anti-mongoloid slant and hypertelorism[1,3]. The maxillary arch is V shaped and slants down posteriorly, resulting in an anterior open bite. This leads to a formation of pseudo-cleft palate[2,7]. It can lead to a flat nasal bridge with a deviated nasal septum[1,3]. The lips are bow shaped and often unable to form a lip seal[3]. Segmentation of embryonic phalanges leads to ossification of the interphalangeal joints causing immobility of digits in syndactyly[3]. This syndrome could give rise to delayed tooth eruption, thick gingiva, severe dental crowding and malocclusion later in life[3]. The reported central nervous system anomalies are megalencephaly and pyramidal tract abnormalities[1,3]. Restricted movements of the glenohumeral joint, elbow joint and vertebral anomalies such as cervical fusion are some of the musculoskeletal manifestations of this syndrome[3]. Visual and hearing problems, mental retardation, cardiovascular, genitourinary and gastrointestinal defects have been reported[3]. The associated dermatological manifestations are acne, hyperhidrosis, hypopigmentation and hyperkeratosis of the plantar surfaces[3].

There are other craniofacial syndromes like Carpenter syndrome and Crouzon syndrome in the differential diagnosis[2,3,4,5]. Table 1 shows a comparison of the main craniofacial syndromes[8,9].

Table 1: ***Comparison of common syndromes with craniosynostosis***

Features	**Apert syndrome**	**Carpenter syndrome**	**Crouzon syndrome**	**Pfeiffer syndrome**
Inheritance	Autosomal dominant.	Autosomal recessive	Autosomal dominant	Autosomal dominant
Involved sutures	Coronal, sagittal, lambdoid		Coronal, sagittal	Coronal, sagittal
Cranium	Craniosynostosis	Craniosynostosis	Craniosynostosis	Craniosynostosis
Cranial shape	Acrocephaly, brachycephaly	Acrocephaly, brachycephaly, oxycephaly	Brachycephaly, scaphocephaly, trigonocephaly	
Morphological manifestations	Midfacial hypoplasia, shallow orbits, proptosis, hypertelorism, down turned mouth, symmetrical syndactyly of hands and feet, choanal atresia, ventriculomegaly, Genitourinary/cardiovascular anomalies	Mild syndactyly of fingers, preaxial polydactyly of feet, hypogenitalism, obesity, congenital heart disease	Midfacial hypoplasia, maxillary hypoplasia, shallow orbits, proptosis, hypertelorism, bifid vulva/ cleft palate	Midfacial hypoplasia, proptosis, hypertelorism, soft tissue syndactyly of second and third digits, malformed enlarged great toes and thumbs
Intelligence	Developmental delay, learning problems, most have reduced intelligence	Mild to moderate lack of intelligence, normal in some	Normal	Normal (type I) Developmental delay (types II & III)

The treatment of Apert syndrome should begin at birth and a multidisciplinary approach is needed with input from a paediatrician, neurosurgeon, plastic and reconstructive surgeon, ophthalmologist, psychiatrist, neurologist and geneticist for the effective planning of treatment. The physiotherapist,

occupational therapist and speech therapist reviewed this baby during the visits to the tertiary care centre and gave their input. Correction of the syndactyly is usually done in the first year of life and completed by three to four years of age[3]. Midfacial hypoplasia could be corrected at 4 to 6 years of age[3]. There is a place for orthodontic and orthognathic (correction of jaw) surgery after eruption of permanent dentition and completion of growth[3]. In the future targeted inhibition of FGFR kinase domain could be a non-surgical option for Apert syndrome[3]. Offering genetic counselling is an important aspect as there is a 50% recurrence risk of having an affected offspring[4,10,11,12].

Patient's/ his family's perspective

At birth, the unexpected malformations led to poor parental participation in management decisions. This unusual appearance of the baby was an unforeseen event for both parents and created a lot of anxiety among them. They worried a lot about the long-term survival of the baby. After repeated counselling sessions both parents were convinced to offer their best support for the baby. There were multiple outpatient consultation visits at the leading tertiary care centre in the country which is located almost 300km from home. They enthusiastically attended this centre and made regular follow up visits to the local clinic. As time passed, both parents were happy about the progress made by their baby. The four-year-old sibling has been showing a lot of affection to him during the local clinic visits. Currently, they are more comfortable to answer the questions raised by their relatives and friends during encounters.

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