Unusual Association Of Apert Syndrome With Schizencephaly

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Citation

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Abstract

Apert syndrome (AS) is one of the varieties of craniostenosis characterized by coronal sutural synostosis, midfacial hypoplasia and symmetrical syndactyly. It may be primary, originating from a sutural pathology, or secondary resulting from dysgenesis of the underlying brain. Various intracranial anomalies have also been described in AS like megalocephaly, hypoplastic white matter, heterotopic gray matter, frontal encephalocele and agenesis of corpus callosum. Schizencephaly is a neuronal migration defect characterized by clefts lined by gray matter extending from ventricle to cortical surface. Association of schizencephaly with Apert syndrome is extremely unusual as the craniosynostosis of Apert syndrome rarely coexist with the cerebrospinal fluid filled cystic spaces of schizencephaly. We report a rare case of AS associated with schizencephaly.

INTRODUCTION

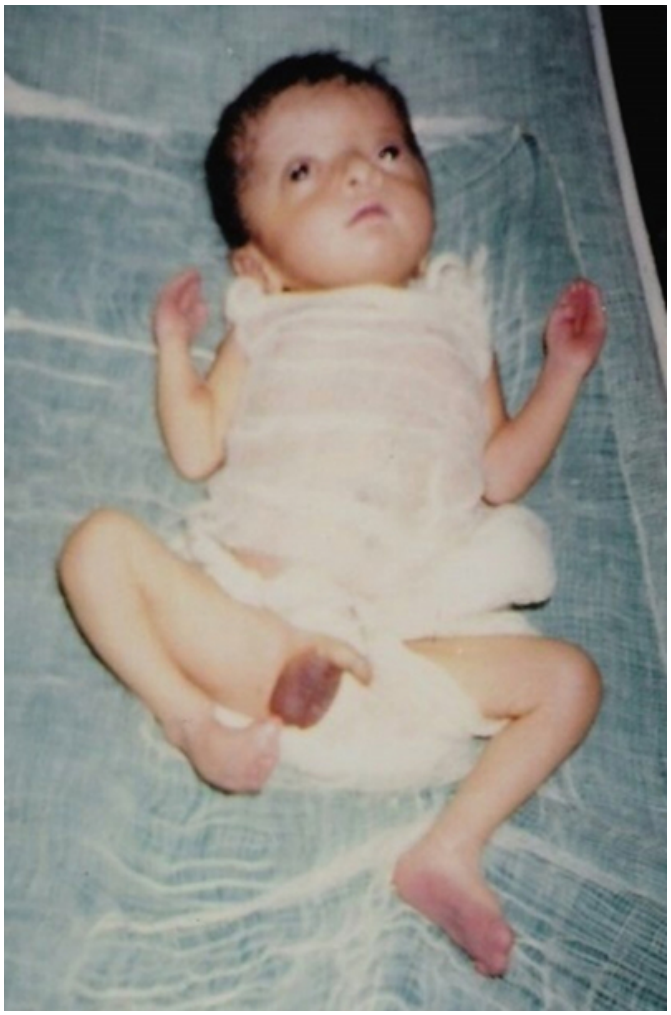
Craniosynososis or craniostenosis is defined as premature closure of the cranial sutures producing deformity of the skull. It may be primary, originating from a sutural pathology, or secondary resulting from dysgenesis of the underlying brain. The incidence varies from 1-2/ 4000 live births. It is found in various syndromes viz. Apert, Crouzon, Pfeiffer and Jackson-Weiss, and is associated with specific systemic anomalies. Apert syndrome (AS), first described in 1906, is one of the most severe of the craniosynososis syndromes and is characterized by coronal sutural synostosis, midfacial hypoplasia and symmetrical syndactyly with a number of intracranial anomalies [1]. We report a rare case of AS associated with schizencephaly.

CASE REPORT

A first-born-male child, product of a non consanguineous marriage, was delivered normally at term in North Bengal Medical College Hospital. The antenatal period was uneventful and the baby cried immediately after birth. On examination, the baby was found to have flattened occiput with frontal prominence, wide open anterior fontanel (4 x 4 cm), shallow orbits with bilateral proptosis, hypertelorism, depressed bridge of the nose, hypoplastic maxillae and low set ears. He had symmetrical syndactyly with complete fusion of all the five digits of hand and feet (Fig. 1).

Figure 1

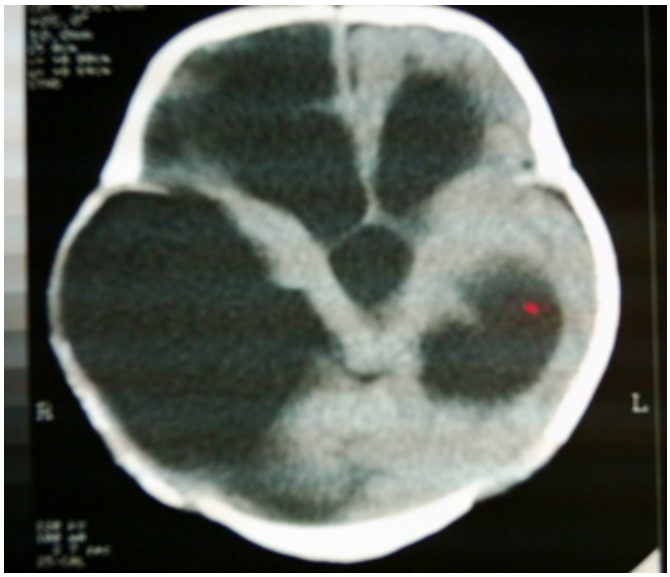
Figure 1: Male baby with Apert Syndrome.



The fused fingers and toes had separate nails. There was no other apparent congenital malformation and systemic examination revealed no other abnormality. Fundoscopy, x-ray of the spine and abdominal ultrasonography were normal. The birth weight was 2.7 kg, length 48 cm, head circumference (H.C.) 36 cm and chest circumference 31 cm. He developed noisy breathing and difficulty in sucking soon after birth and had repeated attacks of apnea since 4th day of life. Nasopharyngeal examination revealed hypoplastic posterior choanae. He was kept in extended neck posture, put on nasogastric (NG) feeding with expressed breast milk and injection theophylline was started. The general condition of the baby improved gradually during hospital stay, apneic attacks became infrequent and spoon feeding was started. H.C. continued to increase and became 39 cm on the 15th day of life. CT scan of the brain showed non development of gray matter in both parietal and occipital region with absence of frontal lobes and corpus callosum giving an impression of open lip type of schizencephaly (Fig. 2).

Figure 2

Figure 2: CT scan of brain showing open lip schizencephaly



Intracranial space was filled with cerebrospinal fluid. Cerebellum and both eyeballs were normal. A diagnosis of Apert syndrome with schizencephaly was made. Karyotyping could not be done due to lack of facility and referral to a higher center was denied by the patient for monetary constraints. He was discharged on the 27th day of life with a H.C. of 42 cm and was called for fortnightly follow up. On follow up, H.C. was found to increase rapidly and at 3 months of age he had a H.C. of 50 cm (> 95th percentile) with brachycephaly. X-ray of the skull showed complete fusion of coronal sutures with wide open sagittal and metopic sutures. He was readmitted and a ventriculoperitoneal shunt was done at the age of 4 months (H.C. of 54 cm), mainly to facilitate nursing. After the shunt surgery, the baby was followed up monthly. H.C. decreased to 50.5 cm at the age of 1 year. None of the developmental milestones were reached even at 14 months and the baby had occasional choking episodes. Unfortunately, at the age of 14 months he developed acute bacterial meningitis and succumbed to death after 23 days of intensive care and therapy.

DISCUSSION

Apert syndrome is an autosomal dominant disorder with incomplete penetration. The defect which is a mis-sense amino acid substitution lies in the chromosome 10q and results in a mutation in FGFR2 gene [$_2$]. A birth incidence of 5.5-16/million live births accounts for 4.5% of all craniostenosis cases. The majority of these are sporadic. Diagnosis is based mainly on typical phenotypic features.

Infants are prone to respiratory insufficiency secondary to airway compromise either in the form of choanal atresia / stenosis or tracheal anomalies. Obstructive sleep apnea may be present because of distorted and malpositioned facial bones contributing to upper airway obstruction. Cleft palate, otitis media and cervical spinal fusion are the commonly associated anomalies. Visceral anomalies in the cardiovascular and genitourinary system have been noted in 10% cases [3]. Intracranial anomalies (72% of the affected children) like megalocephaly, hypoplastic white matter, heterotopic gray matter, frontal encephalocele and agenesis of corpus callosum are frequent. Although ventriculomegaly may be identified on head imaging, significant hydrocephalus with raised intracranial tension is not common, though on occasion it may evolve progressively. Most of these children have developmental delay and cognitive deficits. The present case was probably sporadic in origin as there was no family history. Diagnosis was based on typical physical features of coronal sutural synostosis, brachycephaly, mid-facial hypoplasia and symmetrical syndactyly. There was no visceral anomaly.

Schizencephaly is a rare neuronal migration defect characterized by clefts lined by gray matter extending from ventricle to cortical surface leading to specific lesions. There are two types depending on whether the lips of the clefts are fused or separated. In the closed lip type (type I) cerebral cortical walls on either side of the cleft are in contact with each other. If a wide subarachnoid space separates the two walls, it is known as the open lip type (type II). Pathogenesis of schizencephaly has not been firmly established. The original work of Yakovlev and Wadswoth [4,5] suggests failure of normal migration of the primitive neuroblasts resulting in cerebral cleft. In the normal embryo, beginning seventh week of gestation, neuroblasts are generated in the germinal matrix. At 8th week these primitive cells begin to migrate along radially oriented glial cells to the cerebral cortical regions. During this period, any insult to the centripetal and centrifugal vessels in the region of germinal matrix may cause hypoxemia and infarction resulting in arrest of migration of these neuroblasts. An ischemic episode occurring at the seventh week of gestation has been hypothesized as the etiological factor [6]. In the walls of the cleft, cerebral mantle exhibits heterotopic grey matter indicating hallmark of migration disturbance. Prognosis is related to the extent of involved cortex. Both genetic and acquired factors have been held be responsible for this pathology [7]. Studies using Single Strand Conformation Polymorphism (SSCP) have revealed germline mutation in the homebox gene EMX2 in patients with severe schizencephaly [8,9].

In literature, approximately 70 cases of type II Schizencephaly have been recorded [10,11]. The exact incidence of Type I schizencephaly is not known. In a study of MRI confirmed cases, 50% were type I and the lesions were unilateral in 65% cases [12]. These patients may exhibit a broad range of neurological disabilities, which are presumably related to the amount of brain tissue involved [13]. They may present with intractable seizures and have variable developmental delay. In a series of six patients studied by Barkovich and Norman [12] four had developmental delay and all had motor dysfunction and intractable seizures. While two patients with fused lip type had normal intelligence, the solitary patient with large unilateral cleft had moderate developmental delay and another with bilateral clefts had severe developmental delay. Two patients with full thickness cleft reported by Srikanth et al [6] had intractable seizures and motor dysfunction but normal intelligence. Gross developmental delay was present in our patient. No milestone was achieved till the age of 14 months. To the best of our knowledge, schizencephaly in association with AS has not been reported before. Whether such association was sporadic or by genetic mutation is not known.

CORRESPONDENCE TO

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