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Case Report

Apert syndrome (Acrocephalosyndactyly): a case report

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ABSTRACT

Apert syndrome is named for the French physician. Eugene Apert in 1906 described the syndrome acrocephalosyndactylia. It is a rare autosomal dominant disorder characterized by craniosynostosis, craniofacial anomalies, and severe symmetrical syndactyly of the hands and feet (i.e. cutaneous and bony fusion refers to webbing of fingers and toes). Apert syndrome is characterized by the premature fusion of certain skull bones (craniosynostosis). This early fusion prevents the skull from growing normally and affects the shape of the head and face. In addition, a varied number of fingers and toes are fused together (syndactyly). Most cases of Apert syndrome are sporadic, may result from new mutations in the gene. The purpose of this paper is to report a case of Apert syndrome in a female fetus of 30 weeks with asymmetrical skull confirmed by prenatal ultrasonography. Pregnancy was terminated and fetus was submitted for detailed autopsy in anatomy dissection hall. The findings and review of literature were presented in this article.

Keywords: Apert syndrome, Craniosynostosis, Fibroblast growth factor receptor 2 gene, Midface hypoplasia, Syndactyly, Congenital disorder

INTRODUCTION

Apert syndrome (acrocephalosyndactyly) is a rare developmental malformation characterized by craniosynostosis, mid-face hypoplasia, symmetrical syndactyly of hands and feet. The prodromal characteristics for the typical cranio-facial appearance are early craniosynostosis of the coronal suture, cranial base and agenesis of the sagittal suture. Apert Syndrome is the most widely recognized craniosynostosis syndrome. It was first described by Wheaton' in 1894 and subsequently further cases were reported by Apert. Apert syndrome, named after this French physician "Eugene Apert" who first described it in 1906 and is a relatively uncommon cranio-facial anomaly. According to Cohen, the incidence of Apert's syndrome is about 15 per 1,000,000 live births. Apert's syndrome has been rarely reported from India. It is inherited in an autosomal dominant fashion. It consists of irregular craniosynostosis associated with syndactyly. This congenital disorder characterized by malformations of the skull, face, hands and feet. It is classified as a branchial arch syndrome, affecting the first branchial arch. Disturbances in the development of the branchial arches in fetal development create lasting and widespread effects. In embryology, the hands and feet have selective cells that die, called selective cell death or apoptosis, causing separation of the digits. In the case of acrocephalosyndactyly, selective cell death does not occur and skin, and rarely bone, between the fingers and toes fuse. The gene involved with Apert syndrome is FGFR2 (fibroblast growth factor receptor 2). Normally FGFR genes are involved in the bones formation. There are four FGFR genes, which are numbered 1 through 4. FGFR2 gene mapped is on chromosome 10q25, 10q26. There is no sexual predilection for this syndrome. More prevalent in certain races, highest in the Asians and lowest in the Hispanics.

Major Features of Apert Syndrome

1. Prematurely fused cranial sutures.
2. A retruded midface i.e. abnormal shaped head and face.

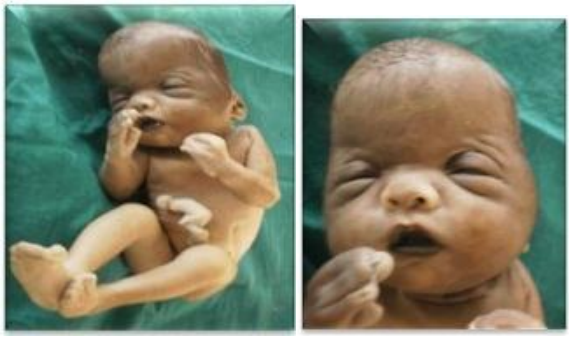
3. Abnormalities of eyes, including down slanting palpebral fissures, hypertelorism, exophthalmoses.
4. Low-set ear sand hearing loss.
5. 5. Malformations of the brain. Hydrocephalus and learning disability.
6. Cleft palate.
7. The skin and bones of the hands and feet are also fused. This is called syndactyly and is usually obvious at birth.

Other related features are

1. Congenital heart defects, Dextrorotation, Pulmonary Artesia and Patent Ductus ateriosus.
2. Tracheoesophageal Fistula and Pyloric stenosis.
3. Polycystic kidneys and bicornuate uterus.
4. Excessive sweating and severe acne.

CASE REPORT

A mother 20 year old with 30 weeks of gestation was admitted to the hospital. She was G2, P1, L1 and healthy and denied illness and use of any drugs. Both the parents were normal and first baby was male child alive and normal. There was no h/o diabetes or hypertension. No h/o of consanguineous. Ultrasonography was done. Single live fetus of 30 weeks with asymmetrical skull was confirmed. With the permission of parents, labor was induced. A female baby delivered normally and was alive for one hour. On examination the baby had craniosynostosis and syndactyly of hands and feet (Figure 1) and was a diagnosed Apert syndrome.



1 2

3 4

Figure 1-4: Apert Syndrome images.

External features

The female fetus was 30 weeks of age. The skull showed craniosynostosis with both coronal sutures fused and agenesis of the sagittal suture. The baby presented with several craniofacial deformities, with asymmetrical face, prominent forehead including midface hypoplasia, hypertelorism, down slanting palpebral fissures, depressed nasal bridge with wide bulbous tip and low set ears. It had flat occiput (Figure 2). A gapping midline defect extending from glabella to lambda (Figure 3, 4). Limb anomalies were present. The upper limbs were more affected than lower limbs. Hands showed mitten appearance. Complex syndactyly was seen involving index, middle, ring and little finger. Left thumb was fused and right thumb flexed and separated with contiguous nail beds (synonychia) (Figure 5). The lower limbs, the feet showed sock appearance. Syndactyly involving 2, 3, & 4th toes with synonychia (Figure 5). Skin showed wrinkling of forehead, interruption of eyebrows and skin dimples at knuckles and shoulders (Figure 2).

Figure 5: Synonychia.

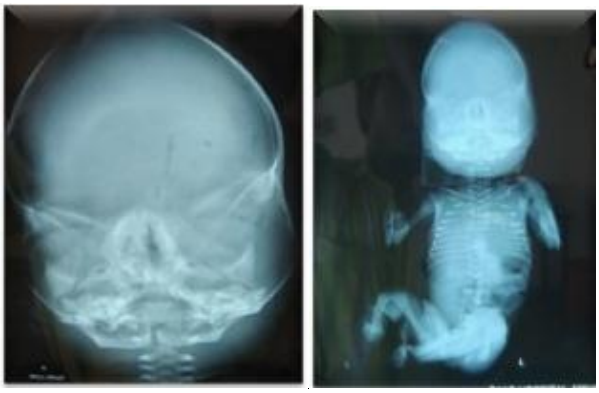


Figure 6-7: Radiological features.

Internal features

Brain was soft and no anomalies were identified. Heart was normal with apex on the left side (Figure 8). Lungs showed hypoplastic with absence of interlobular fissures (Figure 9). GIT with large liver extending entire

hypochondrium and small gallbladder. Stomach and spleen normal in position (Figure 10). Small intestine in the midline & caecum and appendix seen at the left iliac fossa. Rectum was normal (Figure 11). Urogenital system with polycystic kidneys and normal urinary bladder. Uterus, fallopian tubes and ovaries normal (Figure 12).

Figure 8: Horizontally oriented heart.

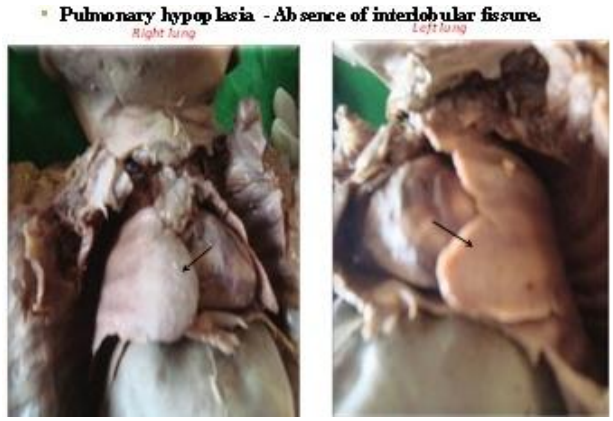


Figure 9: Respiratory system.

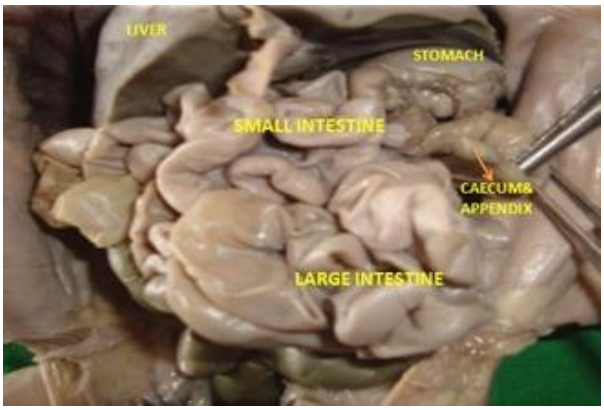


Figure 10: Gastrointestinal tract.

Radiological features

1. Face: Non fusion of mandible, high arched palate & widely placed shallow orbit (Figure 6).

2. Limbs: Syndactyly involving only soft tissue, not involving osseous part (Figure 7).

3. Entire skeleton otherwise normal with no ankylosis or spine fusion (Figure 7).

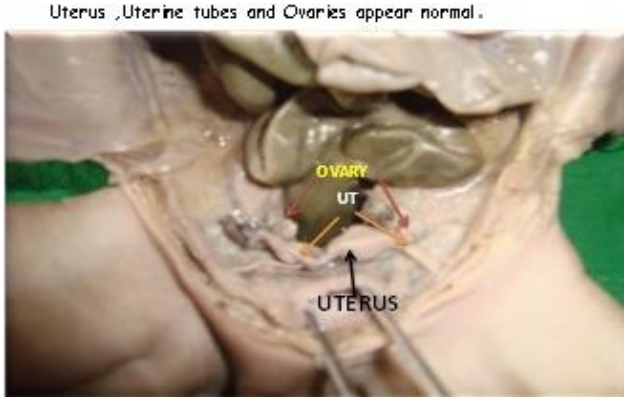


Figure 11: Genital system.

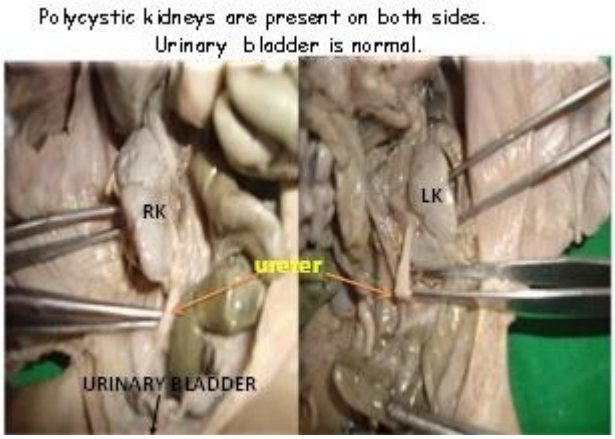


Figure 12: Kidneys.

DISCUSSION

Apert syndrome is named for the French physician who first described it, Eugen Apert in 1906. Apert Syndrome is a genetic defect and falls under the broad classification of craniofacial/limb anomalies.[1,2] Apert syndrome is primarily characterized by specific malformations of the skull, midface, hands, and feet. The skull is prematurely fused and unable to grow normally therefore the midface appears sunken. The fingers and toes are fused together in varying degrees. The index case was associated with all above features. According to Cohen[3] the incidence of Apert's syndrome is about 15 per 1,000,000 live births. It is rarely reported from India.[4] Acrocephalosyndactyly may be an autosomal dominant disorder. It is inherited with mutations of either Ser252Trp or Pro253Arg in fibroblast growth factor receptor 2 (FGFR2) on chromosome 10q25.[5-7] Apert syndrome both has craniosynostosis and syndactyly. The FGFR2 gene under goes point mutation that causes the syndrome in 98% of the patients. The FGFR2 is active at the metaphysis;

diaphysis and also in the interdigital mesenchyme. Mutations in the FGFR2 gene cause Apert syndrome and alters the protein and causes prolonged signaling, which can promote the premature fusion of bones in the skull, hands, and feet. The FGFR2 also is responsible for early fusion of several sutures of the skull. This may explains why both symptoms are always found in Apert syndrome. All acrocephalosyndactyly syndromes show limb abnormalities. The typical hand anomalies of Apert syndrome distinguish it from other craniosynostosis. The hands of Apert's three types i.e. type I (spade), type II (mitten) and type III (rose bud). The present case has type II, mitten variety. The other anomalies, includes cardiovascular (23.5%), cleft palate (23.5%), genital and urinary (5.9%) and central nervous system (5.9%), in some of the patients.[10] Abnormalities of the heart and blood vessels, gastrointestinal tract, kidneys and genital-urinary organs can also occur in Apert syndrome according to Dr. Trisha Macnair. The present case has no cardiovascular anomalies or cleft palate and brain was soft. On the other hand fetus presents with intestinal anomalies, polycystic kidneys and pulmonary hypoplasia associated absence of interlobar fissures.

There is a strong evidence of an abnormal cartilage formation in pathogenesis of development in Apert syndrome. In humans the cartilage abnormalities results in craniosynostosis syndrome as Crouzon, Pfeiffer as well Apert may be due to abnormal migration of neural crest cells in early embryonic stage.[11,12] The offspring of a parent with Apert syndrome has a 50% chance of inheriting the condition. In 1995, A.O.M. Willkie published a paper showing evidence that acrocephalosyndactyly is caused by a defect on the fibroblast growth factor receptor 2 gene, on chromosome 10.[12] It occurs in approximately 1 per 160,000 to 200,000 live births. Males and females are affected equally. It can be inherited from a parent who has Apert, or may be a fresh mutation. This mutation usually occurs in a sperm and Apert syndrome is one of the few genetic conditions linked to older fathers, particularly men over the age of 50.[13] The present fetus was sporadic because both the parents had normal karyotype and parents' age was below 30 years of age. The cause of mental retardation in Apert's syndrome is unclear. The only possibility is that premature closure of cranial sutures, increased cranial pressure and can limits the growth of the brain and hence the intelligence. Cognitive abilities in people with Apert syndrome range from normal to mild or moderate intellectual disability). Additional signs and symptoms of Apert syndrome can include hearing loss, unusually heavy sweating (hyperhidrosis), oily skin with severe acne, patches of missing hair in the eyebrows, fusion of spinal bones in the neck (cervical vertebrae), and recurrent ear infections that may be associated with an opening in the roof of the mouth (a cleft palate).

Early craniotomy is required to prevent premature closure of the sutures. The mental attitude of the index case was not identified because the female baby died one hour after the birth.

CONCLUSIONS

There is no cure for Apert syndrome, but much can be done to prevent or treat complications and help the child grow as normally as possible.

Prenatal Tridimensional Sonographic and Magnetic Resonance Imaging at mid-trimester can diagnose Apert syndrome. For sporadic Apert syndrome a three dimensional computed tomography and molecular biology is preferred. The current role is ultrasound and genetic analysis and counseling is done. Discovery of mutation in FGFR genes now allows the definitive antenatal diagnosis of Apert syndrome and other craniosynostosis syndromes and skeletal dysplasia. If the baby is alive there is a high incidence of raised intracranial pressure, which can first occur at any age up to 5 years and may recur. Causes of raised intracranial pressure include craniocerebral disproportion, upper airway obstruction and hydrocephalus. Careful clinical, ophthalmologic, respiratory, and radiologic monitoring is done and then treated most appropriately. Surgical treatment requires a team approach consisting of neuroradiologist, craniofacial surgeon, pediatric surgeon, pediatric anesthetist, plastic surgeons for hand surgery[14] and orthodontist. The results of this study provide information which will be of help in counseling the families who have a child with Apert's Syndrome.

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