A case report of Apert syndrome

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ABSTRACT

**Introduction:** Apert syndrome (AS) is a rare type 1 acrocephalosyndactyly syndrome, characterized by craniosynostosis, severe syndactyly of the hands and feet, and dysmorphic facial features. It exhibits autosomal dominant inheritance assigned to mutations in the fibroblast growth factor receptor gene.

**Case Illustration:** We presently describe the case of a 14 years old male patient with acrocephaly, prominent forehead, ocular hypertelorism, proptosis, short and broad nose, pseudoprosphoria, crowding of teeth and ectopia, maxillary hypoplasia, low hairline, webbed neck, pectus excavatum, and severe bilateral syndactyly of hands and feet. The examination revealed apical cranium, occipital flattening, enlargement and hypoplasia of the premaxillary opening, crowding, ectopic teeth, tapering of the mandibular apex, and pseudognathia.

**Conclusion:** We reported a 14 years old male patient with AS with craniosynostosis and acrocephalosyndactyly. The characteristics of clinical manifestation of AS should be aware by physicians to be able to diagnose the disease.

**Keywords:** Apert syndrome, craniosynostosis, acrocephalosyndactyly.


INTRODUCTION

Cranial stenosis is premature healing of one or more sutures. Decreased or asymmetrical growth of the skull occurs and the calvaria or base is deformed. In 1851, Virchow found that growth stopped in the direction perpendicular to the affected suture line and continued in the direction parallel to it. Common features include suture fusion, midface hypoplasia, and facial and limb abnormalities. Apert syndrome (AS) is one of the syndromes characterized by craniosynostosis, midfacial hypoplasia, and symmetrical hands and ankles.

Craniofacial abnormalities characteristic of AS include craniofacial malformations, large head (conical dome), prominent forehead, prominent eyes, cranial hypertrophy, and flat nose with low nasal bridge. Oral manifestations can include false clefts, strongly arched palate, horizontal and vertical maxillary hypoplasia, crowding, delayed tooth development, tooth misplacement, disorganized and crowded teeth. The mandible is generally of normal size and shows pseudo growth. Rare conditions affecting the central nervous system, heart, gastrointestinal, genitourinary system, and spinal abnormalities have been reported.

The characteristic facial features of AS, such as a protruding forehead, bulging eyes, sideways gaze, flat nose with a low nasal bridge, hypoplastic maxilla, crooked teeth, webbed neck, short hairline, and fused ribs and limbs, are severe and have been documented in the literature. Here we provide a case report of young patient with clinical characteristic of AS.

CASE PRESENTATION

A 14-year-old male patient consulted to a doctor. Initial examination reveals deformities on the face, limbs, and an interlocking neck. Patients with normal height and weight for their age. A patient's family history was obtained. The patient is the second child and has two female siblings. His male parents are the second of five children where his grandfather is the second of five children. Psychological examination showed no abnormalities. To date, there have been no symptoms associated with the heart or respiratory system. On physical examination, the patient had acrocephaly, prominent forehead, hypertelorism, proptosis, broad nasal bridge, webbed neck, short hairline, funnel chest.

Both eyes of the patients revealed exophthalmos, right eye exotropia, visual acuity of 0.1 could not be corrected, emblyopia. Vision of left eye 1.0. Both eyes often complain that they are often red due to keratitis (Figure 1). We obtained cutaneous syndactyly of both hands, enlarged thumbs, subluxation phalanx of distal of the hand (Figure 2). Total syndactyly of the toes of both feet and brachydactyly was detected (Figure 3).

Radiographic examination revealed apical cranium, occipital flattening, enlargement and hypoplasia of the premaxillary opening, crowding, ectopic teeth, tapering of the mandibular apex, and pseudognathia (Figure 4). On both hands, we obtained syndactyly of the skin flexion, deformity of all fingers, enlargement of the distal phalanx of the thumb, and occasional subluxation of the distal phalanx were noted (Figure 5). There were no abnormalities in the cervical and lumbar spine. From the clinical characteristic and radiology evaluation, the patient concluded with suspicion of AS.

DISCUSSION

Apert syndrome is called acral syndactyly type I, a type of cranial syndactyly. The main features of AS are early cranial synostosis, hypertension, limb synostosis,
and variable phenotypic manifestations. It is an autosomal dominant characteristic and occurs as a mutation in the fibroblast growth factor receptor 2 (FGFR2) gene at the 10q26 locus. The FGFR2 gene encodes a protein called the fibroblast growth factor receptor 2 gene. This protein is one of four FGFRs involved in angiogenesis, wound healing, embryonic development and regulation of cell division, growth and maturation. FGFR binds fibroblast growth factors with higher affinity and plays an important role in the signaling pathways active during craniofacial fusion. The molecular basis of AS is highly specific. Two different types of mutations have been identified in the binding sites between immunoglobulins such as ring 2 and immunoglobulins such as ring 3 on fibroblast growth factor receptor 2 (FGFR2). Furthermore, intracellular signals directed to the FGFR play important roles in embryogenesis and, in their absence, early gastric formation, abnormalities during implantation, impaired epithelial-epithelial interactions in mesenchymal bone, and causes defects in periosteal and endothelial bone formation. Most patients have a normal karyotype. In our country, analysis for certain genetic mutations is done in private medical centers, but in our state this examination is not available.

Paternal mutations are commonly observed, but most cases are sporadic and develop due to new mutations. The incidence ranges from 9.9 to 15.5 per million of her live births, with no gender differences. The phenotypic manifestations of this disease were explained by early healing of cranial sutures. Premature closure of the coronary sutures before 3 months of age resulted in shortening of the anterior-posterior diameter, elevation of the forehead, and swelling associated with cerebral atrophy (cone). The most prominent symptom of this syndrome is limb adhesions. Our patients also had the most obvious symptoms, namely acromegaly, sticky fingers and toes. In these patients, the midface is hypoplastic. Ocular symptoms include glaucoma, protrusion, and oblique palm cleft. The nose and base of the nose are short and wide. Our patients have all specific facial features.
Rarely, injuries to internal organs (kidneys, heart, gastrointestinal tract, genitourinary tract), elbows, shoulders, spinal deformities (vertebral malformations, ankylosing spondylitis, spinal hemiplegia), and often central nervous system abnormalities (brain abnormalities), may occur and have been reported to cause psychosis. Patients with AS may have upper respiratory tract infections, sleep apnea, and malnutrition. Respiratory failure can be severe and requires endotracheal intubation or tracheostomy. In our case there were no symptoms but commonly AS cases have mild dyspnea and snoring, there were no other symptoms indicative of visceral disease. True encephalopathy is observed in patients with AS, whereas psychiatric disturbances are rare.5,7,8 A webbed neck and short hairline were observed during physical examination of our patient, which is rare in patients with AS. These features are the hallmarks of Turner syndrome and Noonan syndrome. The normal height of patients without mental disorders precluded other diagnoses. Spine anomalies and most commonly cervical fusion were observed in her 68% of patients but not detected in our patient.7

The anterior-posterior diameter of the anterior cranial fossa is relatively short due to the anterior displacement of the wing of the major sphenoid, the sloping broad and flat forehead, the prominent temporal region, and the flat occipital region. A protruding forehead and a flat occipital region were observed in our patient. Anterior displacement of the sphenoid and obstruction of the frontal bone prevent the maxilla from developing on all three sides of her. As a result, the height of the maxilla, the width of the nasal cavity, and the height of the nasopharynx are reduced. This anatomical configuration significantly hinders the development of the oropharynx and nasopharynx. Mouth breathing is often observed in these patients, leading to decreased respiratory function. The patient said he was breathing fine, but said he had been snoring for several nights. The anterior-posterior diameter of the orbit depends on the influence of the orbit on the lateral wall of the orbit.8 Differential diagnosis should consider Down syndrome, which is characterized by hypertension, flat nose, short stature, and mental retardation. Oral manifestations are explained by a decrease in diameter, particularly the anteroposterior diameter of the maxilla, resulting in denser teeth and an increased anterior opening of the oral cavity.9

Patients with AS have disabling limb deformities.10 The foot deformity can be referred to as Apert foot in the literature and was divided into three types.11 Our patient was eligible for category 3 if finger adhesions were observed on all toes. In AS patients with hand and foot deformities, we determined that in order to improve the quality of life of these patients, ankle correction is recommended with corrective surgery, including partial amputation can be used for this purpose. The feet of patient with AS are often unsuitable for wearing conventional shoes due to pressure pain and often require surgery.12 In addition to craniosynostosis, other genetic diseases such as Crouzon's syndrome, Carpenter's syndrome (acracranial syndactyly type 2), Chotzen's syndrome, and Pfeiffer's syndrome may occur in the differential diagnosis. A particular relevance for craniosynostosis is correlated with mutations in the FGFR gene.13

Crouzon syndrome, characterized by craniosynostosis and facial deformity, includes head malformation, macrocephaly, brachycephaly, protrusion, protrusion, hypertension, hooked nose, maxillary dysplasia, ears and palate. AS has features similar to Crouzon syndrome. In Crouzon syndrome, unlike AS, the limbs are not affected and craniofacial malformations are less advanced. However, in the United States, some stitches are applied prematurely. The face is asymmetrical, with a more prominent forehead and less prominent eyes. Hand and foot deformities, especially severe cases of finger joints, are their hallmark. Crouzon's syndrome was not expected in patients with prominent extremity involvement. Some authors consider Apert-Crouzon syndrome to be a separate entity. Pfeiffer syndrome is characterized by craniosynostosis and enlarged thumbs and toes. Interestingly, our patient had enlarged thumbs on both hands, similar to that seen in Pfeiffer syndrome, whereas in Carpenter syndrome, a cloverleaf skull with facial paralysis and facial features is typical.14,15,16 Co-occurrence of AS and toes with hypertrichosis anterior in
Carpenter's syndrome has been reported in many cases. Our patient does not have toes like hers. The literature indicates that polydactyly AS can always be associated with Carpenter's syndrome.17

In summary, our patient had signs and symptoms characteristic of AS seen in Pfeiffer syndrome, but she also had another mutation characterized by an enlarged polydactyl thumb. There was AS associated with Carpenter's Syndrome. Syndromes characterized by cranial synostosis are indistinguishable from each other, and their co-occurrence is rarely reported, as we saw in our case. In addition, our case differs from others with its webbed neck and short hairline. Fetal DNA analysis can identify specific mutations when a family history of AS is established. Prenatal diagnosis can be made by showing her FNGR gene mutation at 16 weeks of gestation, showing spondylitis fused and ankylosing spondylitis on prenatal ultrasound. AS is a rare disease with no cure, and it places a physical and psychological burden on patients, their families, and medical institutions. Therefore, the necessary steps are prenatal ultrasound and pregnancy termination.18

Because the manifestations of AS are highly variable, disease diagnosis and management should be performed by a multidisciplinary team in collaboration with neurosurgeons, plastic surgeons, and reconstructive surgeons. A team of physiotherapists, an ophthalmologist, neurologist, endocrinologist, and geneticist is recommended. Diagnosis is based on laboratory, radiological, and genetic tests. There is no definitive cure, but surgical correction of the anatomic deformity may result in cure. Cranial correction and anterior orbital surgery are recommended for infants aged 6–9 months, and reconstructive fusion surgery is generally considered for patient aged 6 years and older. Additionally, these patients present with emotional and behavioral disturbances and may require psychiatric consultation for severe craniofacial abnormalities.18

CONCLUSION
We reported a 14 years old male patient with clinical manifestation of AS with craniosynostosis and acrocephalosyndactyly. Recognizing the clinical manifestation of AS may important for clinicians to have a suspicion of this syndrome, therefore proper further investigation could be conducted and improve the patient’s management.

CONFLICT OF INTEREST
The author reported no conflict of interest.

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PATIENT CONSENT
The patient’s father provided written consent for the case details to be published including the patient’s personally identifiable information.

AUTHOR CONTRIBUTION
NWC responsible to the study’s conceptual, data acquisition, clinical data assessment, follow-up of the patient, manuscript preparation, and manuscript revision.

REFERENCES