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Case Report
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CLINICAL FINDINGS OF 2-MONTHS-OLD BABY WITH APERT SYNDROME: A RARE CASE REPORT

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Abstract
Apert Syndrome is a rare congenital disorder characterized by a premature sutural fusion that can occur as a single abnormality or associated with other anomalies. Mutations are transmitted in the paternal chromosome, which is why advanced paternal age could be a risk factor. We report a 2-months old baby boy came to the ER with shortness of breath and difficulty in nutrition intake caused by choking at home. Physical examination revealed there was more than one congenital abnormalities exist on this patient, including craniosynostosis, prominent frontal region, mid-face hypoplasia, wide set eyes (hypertelorism), downslanting palpebral fissure, ocular proptosis, low-set ears, dysplasia of both ears, symmetrical syndactyly of both fingers and toes, and cleft palate which is revealed in intra-oral examination. Early diagnosis and intervention from multidisciplinary approach is important in improving the outcome of Apert Syndrome.
Keywords: Apert Syndrome, Craniosynostosis, paternal, multidisciplinary

Introduction

Apert Syndrome (AS) was first reported by Eugene Apert, a French pediatrician, who did a few publications in 1906 which described the clinical findings of 9 patients with similar clinical presentation. Moreover, AS was once mentioned in 1842 by Baumgartner, and in 1894 by Wheaton. The incidence rate of this case varies from 1 to 60.000 and reaching up to 200.000 live births and is responsible for 4.5% rate of all craniosynostosis findings, with no sex predilection towards male or female. Advance paternal age has been suspected as the risk factor contributing in the incidence rate of AS.[1]

Apert Syndrome is a congenital disorder characterized by craniosynostosis (early closure of coronal suture), prominent forehead, hypertelorism (abnormally increased distance between the eyes), proptosis, strabismus in some patients, midface hypoplasia, low set ears and defect in the formation of ear structure, cleft palate which is responsible for the difficulty of food intake which can increase the risk of choking, syndactyly of fingers and toes. The abnormality can also happen in the central nervous system including hydrocephalus and ventriculomegaly. Visual and hearing impairment is also found in many cases, which indirectly affects the learning process, although the cognitive impairment is not only caused by AS. Multidisciplinary approach is highly recommended in treating patients with Apert Syndrome comprehensively.

AS is an autosomal dominant disorder with a mutation in fibroblast growth factor receptors (FGFR2) which are unable to give the signal from extracellular fibroblast growth factors (FGFs). Almost every individuals with AS have at least one of the two mutation (S252W or P253R) in the FGFR2 gene on chromosome 10q.[2] Because of this mutation, cells are unable to receive signals required to produce fibrous tissue which is needed for a normal suture to form.

Case Report

A 2-months old baby boy came to the ER with shortness of breath and difficulty in nutrition intake caused by choking at home. The patient look cyanotic when came in and treated in Pediatric ICU (PICU) diagnosed with severe asphyxia with 80% O_2-saturation when first came in, rales are found in both lungs.

The baby was delivered vaginally in 37th week of pregnancy, hence he was born in mature gestational age without complication. Birth weight was 2260

grams (4.9 pounds), length was 48 cm (1.5 feet), with APGAR score of 8 in the first minute of birth and 9 in the first 5 minutes of birth. Family history reveals no congenital abnormalities. The baby was born from a 36 years old father and 29 years old mother and was the first child without a history of medication in pregnancy. The pregnancy was not regularly checked up, hence there was unknown history of complication in the pregnancy.

Physical examination revealed there was more than one congenital abnormalities exist on this patient, including closed coronal suture (craniosynostosis), prominent frontal region, mid-face hypoplasia, wide-set eyes (hypertelorism), downslanting palpebral fissure, ocular proptosis, low-set ears, dysplasia of both ears, symmetrical syndactyly of both fingers and toes (Figure 1), and cleft palate which is revealed in intra-oral examination. Normal muscle tone was found in this patient.

Molecular analysis workup – eg. FRGR2 chromosome –, head CT, echocardiography and X-Ray of fingers and toes was not carried out because of the cost limitation from the patient's family. Blood laboratory studies didn't show significant result, but leukocytosis of 15.000 was found. Therapies only aim to improve patient's quality of life.

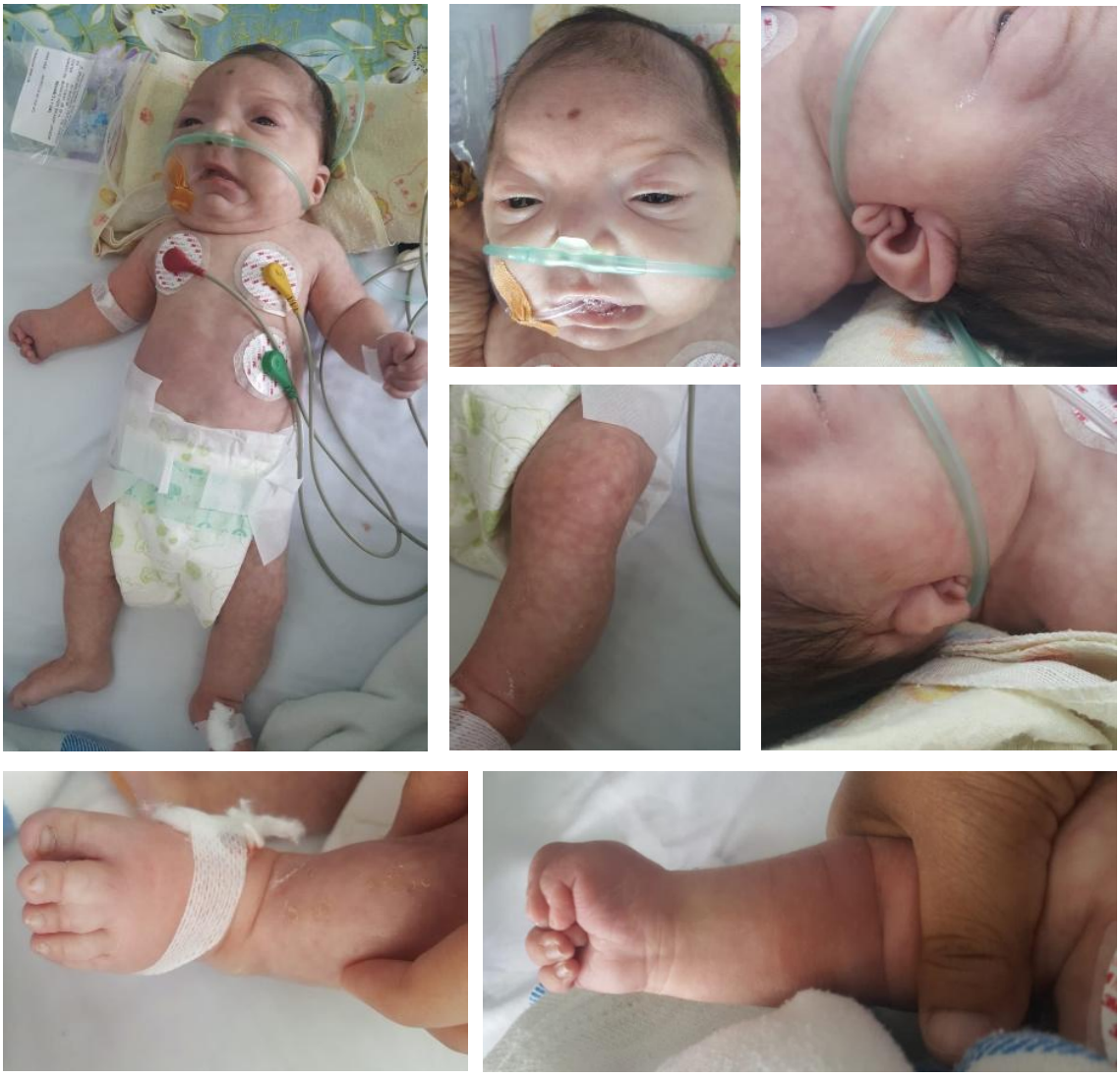

Figure 1: Clinical presentation obtained from physical examination. (A. Whole body presentation; B. Abnormalities in head and face in the form of prominent frontal region, midface hypoplasia, wide set eyes (hypertelorism), downslanting palpebral fissure and ocular proptosis; C. Abnormality in ear in the form of low set ears and dysplasia of the ears; D. Abnormalities in extremities shown by symmetrical syndactyly in fingers and toes

Discussion

Craniosynostosis is one of the most common physical feature found in Apert Syndrome. Craniosynostosis happened because of mutation in gene fibroblast growth factor receptors (FGFR2) which can also happen in other diseases like Crouzon Syndrome, Pfeiffer Syndrome, Beare-Stevenson Syndrome, and Jackson-Weiss Syndrome.[1,3,4] Craniosynostosis can be the only abnormalities who are present, or accompanied by other. AS is a rare autosomal dominant disorder which more than 98% cases happened in de novo mutation. The cause of this mutation is transmitted through paternal-chromosome, hence, increasing age of father in the time of conception may be one of many factors which increase the risk of AS occurrence.[1,5,6] Other contributing factors in AS are viral infection during pregnancy, intake of certain drugs during pregnancy, inflammation, and disruption of the formation of the skeletal. [7,8]

Prenatal diagnosis of AS depends on ultrasound during pregnancy with findings of head-shape abnormalities including closure of coronal suture, midfacial hypoplasia, and syndactyly in fingers and toes.[1,9] Diagnosis can be acquired through clinical presentation and gene mapping to confirm the outcome of physical examination. AS has almost the same symptoms as Crouzon Syndrome. The difference between those two is syndactyly are found in AS, which isn't found in Crouzon. Fusion in the spine usually occur in C5 to C6 in AS, but happens in C2 to C3 in Crouzon. Pseudocleft palate is usually found in AS but isn't found in Crouzon.[5]

Other abnormalities are structural abnormalities in the central nervous system including ventriculomegaly, which are found in 48% of all AS cases.[5,10] Other studies reported that findings can be found up to 60%.[5,11] Most of them are non-progressive ventriculomegaly, this happens because the involvement of sagittal and lambdoid suture, and the stenosis of jugular foramen are rarely occurred in the comparison of Crouzon Syndrome.[5,12,13] Even though the bicoronal synostosis happens usually early, the ventriculomegaly is usually non-progressive because of the above. Studies shown that ventriculomegaly usually disappear when the patient reach five years of living, this happens because of the development of collateral vein as time goes by. This phenomenon can be found in achondroplasia, and this explains the reason why achondroplasia patients rarely need shunting.[5]

Patients with Apert Syndrome usually needs evaluation from more than one specialty including neurosurgery, neuropediatrics, stimulation therapy, ophthalmology, cardiology otorhinolaryngology, plastic surgery, and orthopedics. In this case, gene mapping of FGFR2 gene are not carried out because of the cost limitations from the patient's side, but this workup is essential in diagnosing Apert Syndrome. [1]

Complications that can occur in the manner of late diagnosing including disturbance in the brain's growth, mental retardation, worsen facial deformity, prognathic mandible, and else. Surgical options for syndactyly are usually intended for cosmetic purpose but are irrelevant in improving function in a meaningful way. Surgical options are opted for syndactyly with the intention of normalizing the bone growth, if surgical therapy is adjourned it will worsen the deformity in hands and feet that are already abnormal.[7,14]

Neurocognitive disturbance can occur in AS patients with different severity in each patient. Ranier et al[15] found that 32% patient with AS has IQ greater than 70, in comparison with a study conducted by Patton et al[16] who found 48% patients and Yacubian-Fernandes et al[17] who found the greater number by 77.8%. Lack of education from family and social environment playing a bigger role in lack of cognitive ability in AS patients was found out by Yacubian-Fernandes et al[17], in comparison with skeletal impairment and patient's age when skeletal surgery is performed. However, some studies had shown that early surgery may be able to enhance neurocognitive development in AS patient.[18] Mental retardation in AS patient is a series of combination from a lot of factors, and early surgery plays a role in it.[19]

Variety of anatomical abnormalities in AS patient give the bigger challenges to the physician in treating the condition in a multidisciplinary manner to ensure in maximal function (table 1). Adequate assessment is needed to repair both syndactyly and bone abnormalities,[20] and after the degree of severity has been determined (table 2), surgical correction can be done properly. Some study center suggests that early correction can be done as early as the patient entering 3 months old and as late as 9 months old.[21] But worldwide, usually the correction is done when the patient is entering 6 months old.[22]

Table 1: Management Protocol for Apert Syndrome[23]

Age	Protocol
Birth – 4 months	Complete Multidisciplinary Assesment
4 to 6 months	Fronto-Orbital Advancement Surgery
6 months to 1 year	Posterior Vault Expansion, if needed
2 to 6 years	Annual assesment by craniofascial team
6 to 7 years	Monobloc advancement or Le Fort III osteotomy, facial bipartition (if needed), nasal augmentation (if needed)
6 to 8 years	3 to 6 months checks
8 year to teenager	Orthodontics, annual assesment by craniofacial team
Teenage	Le Fort I osteotomy, Bilateral Sagital Split Osteotomy (BSSO) if needed, genioplasty (if needed)
Late Teenage	Final Assesment, revisionary and touch up procedures

Table 2: Upton's Classification of the Apert Hand[20]

Deformity	Type I	Type II	Type III
Thumb Radial Clinodactyly	Present	Present	Present
Index Radial Clinodactyly	Absent	Present	Present
First Web Syndactyly	Simple (Non-Osseus)	Simple (Non-Osseus)	Complex (Osseus)
Complex 2-3-4 Syndactyly & Symbrachyphalangism	Present	Present	Present
4-4 Syndactyly	Simple,Incomplete	Simple,Incomplete	Simple, Complete

Oral hygiene is also one of the challenges that may occur in AS patients, because fingers abnormalities may cause difficulty for the patients to brush their teeth, hence the electric toothbrush and fluoride mouth rinse may help. An annual dentist checkup is highly recommended to be done.[24]

Conclusions

This case report has shown the clinical findings that can occur in Apert Syndrome, which is a rare congenital abnormalities. Mutations are transmitted in the paternal chromosome, which is why advanced paternal age could be a risk factor. Multidisciplinary approach is needed to improve patient's quality of life, especially with a big cleft palate gap, surgical correction is urgently needed to help the patient's with nutrition intake problem. Early diagnosis and intervention from multidisciplinary approach is important in improving the outcome of AS patients.

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