(Jurnal Plastik Rekonstruksi, 2021; Vol 8, No 1, 1-6)



*CASE SERIES*

# APERT SYNDROME: CASE SERIES AND REVIEW OF THE LITERATURE

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**ABSTRACT**

**Summary:** Apert syndrome is a type 1 acrocephalosyndactyly, a rare syndrome characterized by the presence of multiple craniosynostoses, dysmorphic facial manifestations, and syndactyly of hand and feet. It affects 1:100.00 of birth and the second most common of syndromic craniosynostosis. Molecular genetic tests that identify the heterozygous pathogenic variant in FGFR2 genes - identical with Apert syndrome cost too high to be applicable in developing countries. Therefore, the diagnosis of Apert syndrome should be suspected from the clinical findings. Three cases from the Community of Indonesian Apert Warrior Group were collected. These series were based on medical and surgical records. We obtained the patient characteristic from the phenotypic manifestations only.
We present cases of 6-years-old male, 2-years-old female, and 3-years-old female, respectively, with similar anatomical findings, such as skull shape abnormality, midface hypoplasia, intraoral disfigurement, and hands and feet deformities that resemble Apert Syndrome. Our series presents similar Apert syndrome characteristics, such as typical craniofacial dysmorphic with symmetrical syndactyly of both upper and lower extremities. These clinical findings are essential to establish an initial diagnostic of Apert Syndrome.
***Keywords**: Apert syndrome; Craniosynostosis; Syndactyly*

**ABSTRAK**

**Ringkasan:** Sindrom apert merupakan sindrom acrocephalosyndactyly tipe 1 langka yang ditandai dengan adanya beberapa kraniosinostosis, manifestasi wajah dismorfik yang khas, dan sindrom pada tangan dan atau kaki. Insidensi kelainan ini yaitu 1: 100.000 kelahiran dan merupakan kelainan tersering kedua dari seluruh sindrom kraniosinostosis. Tes genetik molekuler untuk mengidentifikasi varian heterozigot pada FGFR2 yang identik dengan sindrom Apert masih terlalu mahal untuk diterapkan di negara berkembang. Sehingga, diagnosis sindroma Apert harus ditegakkan dari gambaran klinis.
Tiga kasus dikumpulkan dari Komunitas Apert Indonesia. Laporan kasus berdasarkan catatan medis dan bedah. Kami mengumpulkan karakteristik dari manifestasi fenotip.
Kami menyajikan kasus laki-laki 6 tahun, perempuan 2 tahun, dan perempuan 3 tahun masing-masing, dengan temuan anatomi yang serupa, seperti kelainan bentuk tengkorak, hipoplasia tengah wajah, cacat intraoral, serta kecacatan tangan dan kaki menyerupai Sindrom Apert. Pasien menunjukkan karakteristik sindrom Apert yang serupa, seperti dysmorphics kraniofasial khas dengan sindrom simetris pada ekstremitas atas dan bawah. Temuan klinis ini cukup untuk menetapkan diagnosis awal Sindrom Apert.
***Kata kunci**: Sindrom Apert; Kraniosinostosis; Sindaktili*

**Conflicts of Interest Statement:**
The author(s) listed in this manuscript declare the absence of any conflict of interest on the subject matter or materials discussed.

Received: 14 12 2020, Revised: 15 12 2020, Accepted: 11 03 2020

 P-ISSN 2089-6492; E-ISSN 2089-9734 | DOI: 10.14228/jprjournal.v8i1.316

## INTRODUCTION

Wheaton first reported Apert syndrome in 1894, and French pediatrician Eugene Apert in 1906.[1,2] Apert syndrome affects 1:100.000 and is the second most common form of syndromic craniosynostosis.[3] This syndrome is a form of acrocephalosyndactyly type 1 with autosomal inheritance characterized by acrocephaly of brachyshenocephalic type and syndactyly of the hands and feet.[3]

Unfortunately, consensus clinical diagnostic criteria for Apert syndrome have not been published. A molecular genetic test identifying a heterozygous pathogenic variant in FGFR2 identical to Apert Syndrome is recently done in well-developed countries.[4,5] But the cost is still too high to be applicable in developing countries. Therefore, the initial diagnosis of Apert syndrome should be suspected in individuals with suggestive findings such as multiple craniosynostoses, typical dysmorphic facial manifestations, and syndactyly of hand and feet with bone involvement.[5]

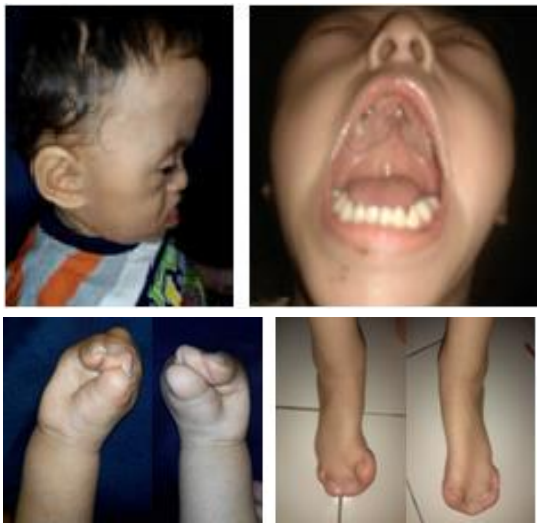
Herein, we present three cases of Apert Syndrome collected from the Community of Indonesian Apert Warrior. The purpose of this report is to present Apert Syndrome patients by highlighting the clinical manifestations.

## CASE REPORT

This retrospective study involved three cases collected from the Community of Indonesian Apert Warrior Group. We report the cases based on the medical and surgical records and collect the phenotypic manifestations' characteristics.

**Case 1**

A 6-year-old-male with Apert syndrome examination revealed a brachycephaly, midface hypoplasia, hypertelorism, proptosis, downslanting palpebral fissures, depressed nasal bridge. Intraoral examination revealed upper and lower alveolar bases were normal, V-shaped maxillary arch and pseudocleft palate. He had bilateral symmetrical syndactyly with complete fusion of all five digits of both upper and lower extremities but with separated nails. (**Figure 1**).



***Figures 1*** Case 1: Facial disfigurement due to midface hypoplasia (upper left), V-shaped maxillary with the pseudocleft palate (upper right), symmetrical complex syndactyly of hands and feet (lower left and right)

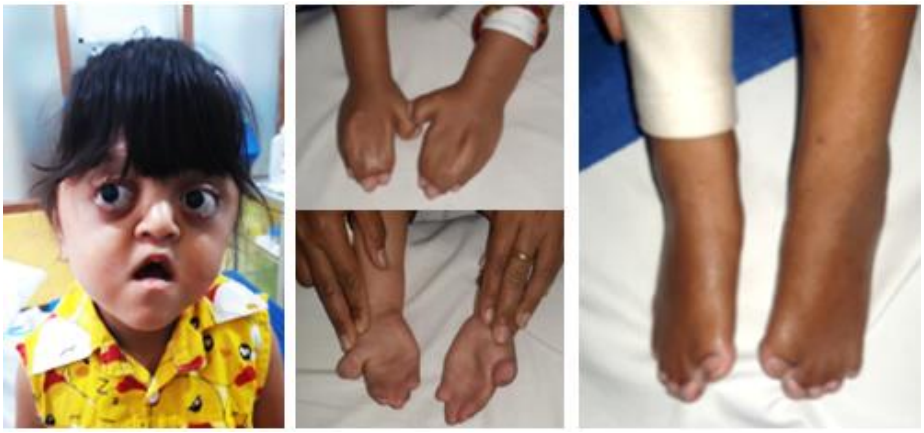
**Case 2**

A 2 years old girl with Apert syndrome, examination revealed brachycephaly, midface hypoplasia, hypertelorism, proptosis, downslanting palpebral fissures, depressed nasal bridge. Intraoral examination revealed palatoschisis. She had bilateral symmetrical syndactyly with the fusion of digits 2-5 of both hands with separated thumb and complete syndactyly of both feet. The fused fingers and toes had separate nails. The patient had no other apparent congenital malformation. **(Figure 2)**

**Case 3**

Presently described is a case of 3 years old female diagnosed with Apert syndrome previously and underwent multiple cranial surgeries. There was no history of abnormal physical findings or syndromic disorder in the whole family. The examination revealed similar typical characteristics of Apert syndrome. She had bilateral symmetrical syndactyly with complete fusion of all five digits of both hands and feet with separated nails. She also had multiple separation procedures for syndactyly of digits 2-4 of both hands. (**Figure 3)** Her hand

Received: 14 12 2020, Revised: 15 12 2020, Accepted: 11 03 2020



***Figures 2.*** Case 2: midface hypoplasia with apparent hypertelorism and proptosis (left), complete symmetrical syndactyly of all digits forming cup-shaped hands (middle), and complete syndactyly of feet with separated nails (right)

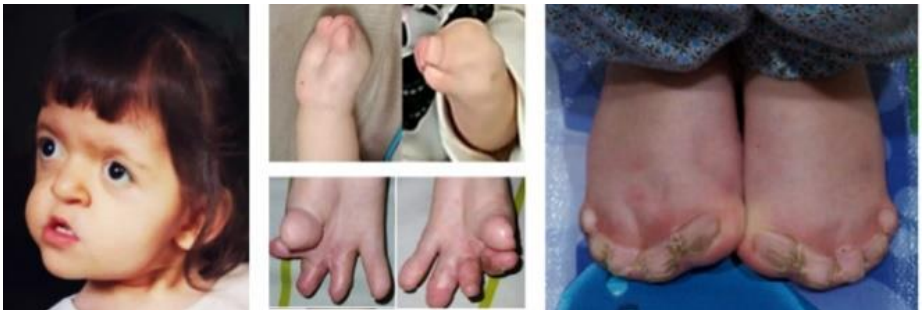


***Figure 3***. Case 3: typical facial dysplasia of Apert syndrome (left), previously bilateral rosebud hand syndactyly (upper middle) had been surgically released (lower middle), complete syndactyly of feet (right)

performed good grip function but with limited movement. The patient had had posterior decompression at 21 months old following FOA (fronto-orbital advancement) surgical procedure at 10 months old. (**Figure 4)**

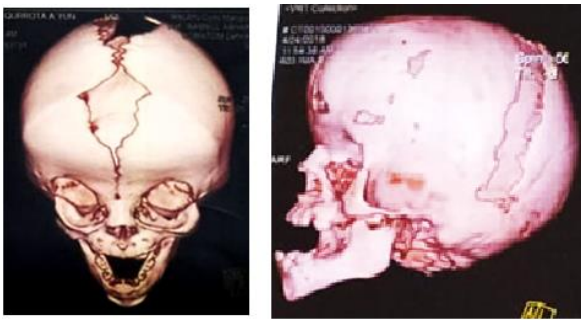


***Figure 4***. CT imaging exhibited premature fusion of anterior fontanelle (left). 3 months after posterior decompression showed partial ossification. (right)

## DISCUSSION

The abnormal skull and facial growth produce its main signs and symptoms: skull deformities, hypertelorism, and midface hypoplasia.[4,5,6,7] Phenotypic manifestations of the disease are explained by premature fusion of cranial sutures.[7,8,9] Premature fusion of the skull bones prevents the head from growing normally, which leads to a sunken appearance in the middle of the face (midface hypoplasia), beaked nose, prominent or flat forehead, proptosis, hypertelorism, flattened nose with a low bridge, and low-set ears. The midface in Apert syndrome is underdeveloped and retruded; a subset of affected individuals has a cleft palate. Oral signs may be enumerated as cleft palate while several with the high arched palate (pseudocleft).[7,8,9] Other oral manifestations include transverse and sagittal maxillary hypoplasia, dental crowding, delay in dentition, ectopic teeth, disarrayed teeth, and teeth crowding enumerated.[10]

Multiple patterns of premature fusion of cranial vault sutures exist in Apert syndrome, which is ideally judged by cephalometry examination.[10,11] Almost all affected individuals have coronal craniosynostosis, and a majority


P-ISSN 2089-6492; E-ISSN 2089-9734 | DOI: 10.14228/jprjournal.v8i1.316

**Table 1**. Description of clinical findings

| No | Craniosynostosis | Deformity | Syndactyly | Imaging |
|---|---|---|---|---|
| Case 1 | Yes | Brachycephalicmidface hypoplasia<br>Pseudo cleft palate<br>V maxillary shape | Symmetrical<br>- syndactyly of digit 1-5 of both hands<br>- fusion of fingernail 1-5<br>- syndactyly of all toes | Never |
| Case 2 | Yes | Brachycephalic<br>Midface hypoplasia<br>Palatoschizis | Symmetrical<br>- syndactyly of digits 2-4 of both hands with separated thumb<br>- syndactyly of all toes | X-ray shows fused 4 fingers 2-4, separated thumb. Bilateral syndactyly of both feet with separated nails |
| Case 3 | Yes | Brachycephalic<br>Midface hypoplasia | Symmetrical<br>- syndactyly of digits 1-5 of both hands<br>- syndactyly of all toes | MSCT Scan cerebral without contrast shows premature closure of the coronal suture<br>Other MSCT show different AP diameter before and after surgery (FOA, Posterior decompression) |

**AP = anteroposterior, FOA = FrontoOrbital Advancement*

also have involvement of the sagittal and lambdoid sutures.[10,11,12] Bilateral coronal

synostosis is the most common type found in the patient with Apert Syndrome. Apert cranial base angulation is inconsistent as well.[11,12] However, the skull deformity in Apert's syndrome is not always typical or characteristic, and it is not always in the same type.[12,13] It may either brachycephalic–too wide (premature closure of the coronal and or lambdoid sutures), scaphocephalic-vertically elongated (premature closure of sagittal suture), turricephalic-tower shaped (premature closure of all sutures), plagiocephalic-asymmetrical (asymmetrical premature closure of all suture in one half of the head).[12,13] In our cases, all have brachycephalic skull shapes (**Table 1).**

In the differential diagnosis of other craniosynostosis disorders, we compared other genetic disorders that can be seen apart from craniosynostosis syndrome include Crouzon, Carpenter (acrocephalosyndactyly type 2), and Pfeiffer syndromes. Apert Syndrome mainly demonstrates similar characteristics with Crouzon syndrome. Although Crouzon syndrome is characterized by craniosynostosis and dysmorphic craniofacial structures in our cases, we did not think of Crouzon syndrome due to the involvement of extremities abnormality. In the Crouzon syndrome, contrary to Apert Syndrome, extremities are not involved, and craniofacial deformities lead a milder course.[13] Pfeifer syndrome is also characterized by craniosynostosis, but with broad and medially deviated thumb and enlarged toes as well, but those characteristics were not present in our patients.[13]

The hand in Apert syndrome always includes a fusion of the middle three digits; the thumb and fifth finger are sometimes also involved.[13,14] Synonychia (fusion of ≥2 nails) of the second through fourth fingers is common. The appearance is sometimes referred to as a "mitten hand".[14]

The Upton classification is most commonly used; it divides the hand deformity into 3 types that correspond with its severity.[16] In type I (spade hand), the thumb is separated from the index by a shallow web space; in the fifth finger webspace, the syndactyly is always simple, and the transverse metacarpal arch is normal. In type II (spoon hand), there is partial or complete simple syndactyly of the first webspace, the simple syndactyly in the fourth interdigital space is usually complete, the border digits are in marked rotation, and the palm is concave. In type III (rosebud hand), there is complex syndactyly with distal synostosis between the thumb and the index finger, and broad, conjoined nail overlies the bony fusion among the thumb, index, long, and ring fingers.[16].

Anatomical deformities corrective surgery can provide a cure. In general, multi-suture craniosynostosis should be surgically repaired in the first year of life. In case number 3 had surgical procedures of FOA and posterior decompression at the age of 6 months. This operation's results need to be evaluated further


P-ISSN 2089-6492; E-ISSN 2089-9734 | DOI: 10.14228/jprjournal.v8i1.316

whether the operative action results in progressive function and better anatomy (compared to those that do not).

Most children with Apert will require surgical reconstruction and physical-occupational therapy to maximize the use of their hands secondary to hand surgeries. The timing of surgical corrections varies with the complexity of the deformity and the webspace involved.

## SUMMARY

Our patients present similar characteristics of Apert syndrome. These include brachycephaly, midface hypoplasia, hypertelorism, V-shaped maxillary, cleft abnormality, and symmetrical syndactyly of both hands and feet. The three classical characteristics of Apert syndrome were present (craniosynostosis, typical facial deformities, and symmetrical syndactyly of both hands dan feet). These clinical findings are sufficient to establish an initial diagnostic of Apert syndrome.

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## ACKNOWLEDGEMENT

The authors acknowledge the Indonesian Apert Warrior Community for the spirit of being a part of Apert survivors and for the great support to this case report.

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P-ISSN 2089-6492; E-ISSN 2089-9734 | DOI: 10.14228/jprjournal.v8i1.316

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P-ISSN 2089-6492; E-ISSN 2089-9734 │ DOI: 10.14228/jprjournal.v8i1.316