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Dissecting The Clinical Phenotype of Apert Syndrome

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ABSTRACT

We report two clinically and genetically confirmed cases of Apert Syndrome to emphasize the diagnostic relevance of detailed phenotypic evaluation in early identification of this rare craniosynostosis syndrome due to pathogenic variants in the FGFR2 gene. The first case is a 14-year-old male who presented with severe growth retardation, craniofacial dysmorphism, classic mitten-hand syndactyly; he also had a de novo pathogenic FGFR2 variant (c.755C>G, p.Ser252Trp). The second case is a 1.5-year-old male who presented with early signs of turri-brachycephaly, midfacial hypoplasia, rosebud hands, microcephaly, and had a pathogenic FGFR2 variant (c.758C>G, p.Cys253Trp). The in-depth phenotypic analysis in both cases emphasizes the need to capture specific craniofacial and limb features with surgical input, as these features often enable prompt diagnosis of the disorder and expedite genetic testing, counseling, and multidisciplinary care in individuals with Apert Syndrome.

Keywords: Apert Syndrome, Acrocephalosyndactyly type I, FGFR2 gene, Genetic syndrome, Craniosynostosis, Mitten hands/feet, Syndactyly

Abbreviations

FGFR2- fibroblast growth factor receptor 2

SD- Standard Deviation

BMI- body mass index

We present two cases of Apert Syndrome.

CASE 1

A 14-year-old male presented with complaints of abnormal facial appearance since birth and growth delay. He is the firstborn child of a nonconsanguineous marriage. He was delivered at home through normal vaginal delivery and cried immediately after birth. Mother's age at conception was 21 years, and there is no family history of

similar features. On Clinical examination, it was noted to have bilateral mitten hands and feet (syndactyly), craniosynostosis, hypertelorism, and midfacial hypoplasia with crowding of teeth and a high-arched palate. The weight of the patient at the time of presentation was 22.4kg (less than -3 SD), the height was 134cm (less than -3 SD), and the BMI was 12.47kg/m2 (less than -3 SD), indicating severe growth retardation. (3) Genetic analysis confirmed the presence of a pathogenic heterozygous variant in the FGFR2 gene (c.755C>G, p.Ser252Trp), confirming Apert Syndrome. Parenteral segregation analysis confirmed this variant to be de novo in occurrence. Genetic counseling was provided to the family, explaining the autosomal dominant inheritance pattern and the low recurrence risk for future pregnancies.

Figure 1 . Clinical features of a 14-year-old male with Apert Syndrome. (A)) Frontal facial view highlighting turribrachycephaly, hypertelorism, proptosis, midface hypoplasia, and a depressed nasal bridge (B) Lateral head view showing midfacial hypoplasia, high-arched palate, and dental crowding (C) Dorsal view of the feet displaying bilateral syndactyly with a mitten-like appearance. (D) Dorsal view of the hands illustrating bilateral syndactyly with fused digits, consistent with the mitten-hand deformity.

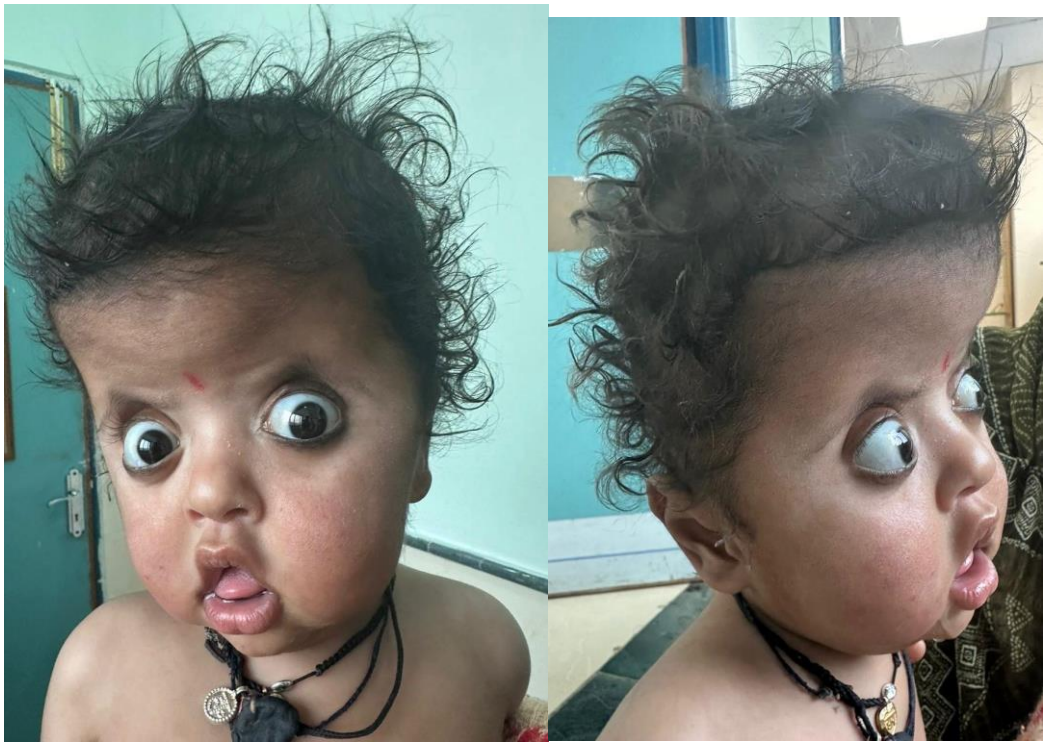
CASE 2

A 1.5-year-old male who presented with complaints of delayed growth and development with abnormal facies and limb anomalies. He is the second-born child of a nonconsanguineous marriage without significant natal events. His facial phenotype showed the presence of craniosynostosis with turri-brachycephaly of the skull. Eyes showed hypertelorism, shallow orbits with proptosis. Ears were low set with the presence of bilateral conductive hearing loss. He had midfacial hypoplasia with a depressed nasal bridge and parrot beak appearance of the nose. His dentition was delayed with malocclusion and a protruded tongue. Extremities showed the presence of brachydactyly with type 3 syndactyly (rosebud hand) with synonychia and deeply concave palm with loss of plantar creases in both feet. His genito-urinary and cardiovascular systems were normal. Anthropometry examination showed present weight 7.8 kg (-2 to -3 SD), length 74.8 cm (-2 to -3 SD), and head circumference 38 cm (<-3 SD), showing microcephaly. His genetic analysis confirmed the presence of a heterozygotic pathogenic variant in the FGFR2 gene (c.758C>G, p.Cys253Trp) at location Exon 7.

Apert Syndrome (Acrocephalosyndactyly Type I) is a rare genetic disorder most commonly caused by de novo missense variants in the fibroblast growth factor receptor 2 (FGFR2) gene, primarily c.755C>G (p.Ser252Trp) and c.758C>G (p.Pro253Arg) in exon 7 on chromosome 10q26.[1] The disorder is usually sporadic and occurs as a de novo mutation, but can also be inherited in an autosomal dominant manner with full penetrance.[1] This mutation upregulates the FGFR2 gene, which, in turn, causes greater precursor cell consolidation into osteoblasts. This results in excessive subperiosteal bone matrix deposition, leading to advanced ossification of the calvaria. Cranial premature suture fusion (craniosynostosis) limits growth perpendicular to the suture-affected area and results in fusion of bones into one single solid structure, with compensatory growth occurring at remaining open sutures to form a more dome-like structure.[3] The condition affects males and females equally, and its occurrence significantly increases with advanced paternal age.[4]

Craniosynostosis syndromes such as Crouzon Syndrome, Pfeiffer Syndrome, and Saethre-Chotzen Syndrome need to be considered in the differential diagnosis of Apert Syndrome. Crouzon Syndrome, also caused by FGFR2 variants, presents similarly with features of craniosynostosis combined with midfacial hypoplasia but stands out due to the lack of syndactyly, which pneumonically defines Apert Syndrome.[5] Pfeiffer Syndrome, caused by variants in FGFR1 or FGFR2, shares craniosynostosis and syndactyly but is differentiated by broad thumbs and toes, which are absent in Apert Syndrome.[6] Saethre-Chotzen Syndrome, associated with TWIST1 variants, shows craniosynostosis and mild syndactyly but classically manifests with ptosis and a low hairline, differentiating it from Apert Syndrome.[5]

A multidisciplinary team of pediatricians, geneticists, neurosurgeons, craniofacial surgeons, orthodontists, otolaryngologists, and psychologists is needed for treatment.[3] To enhance functional outcome, procedures like cranial vault remodeling and syndactyly release are often performed, along with devices for conductive hearing loss.[4] Long-term prognosis depends on the severity of skeletal and neurological involvement, along with the availability of timely, comprehensive medical care.[6]



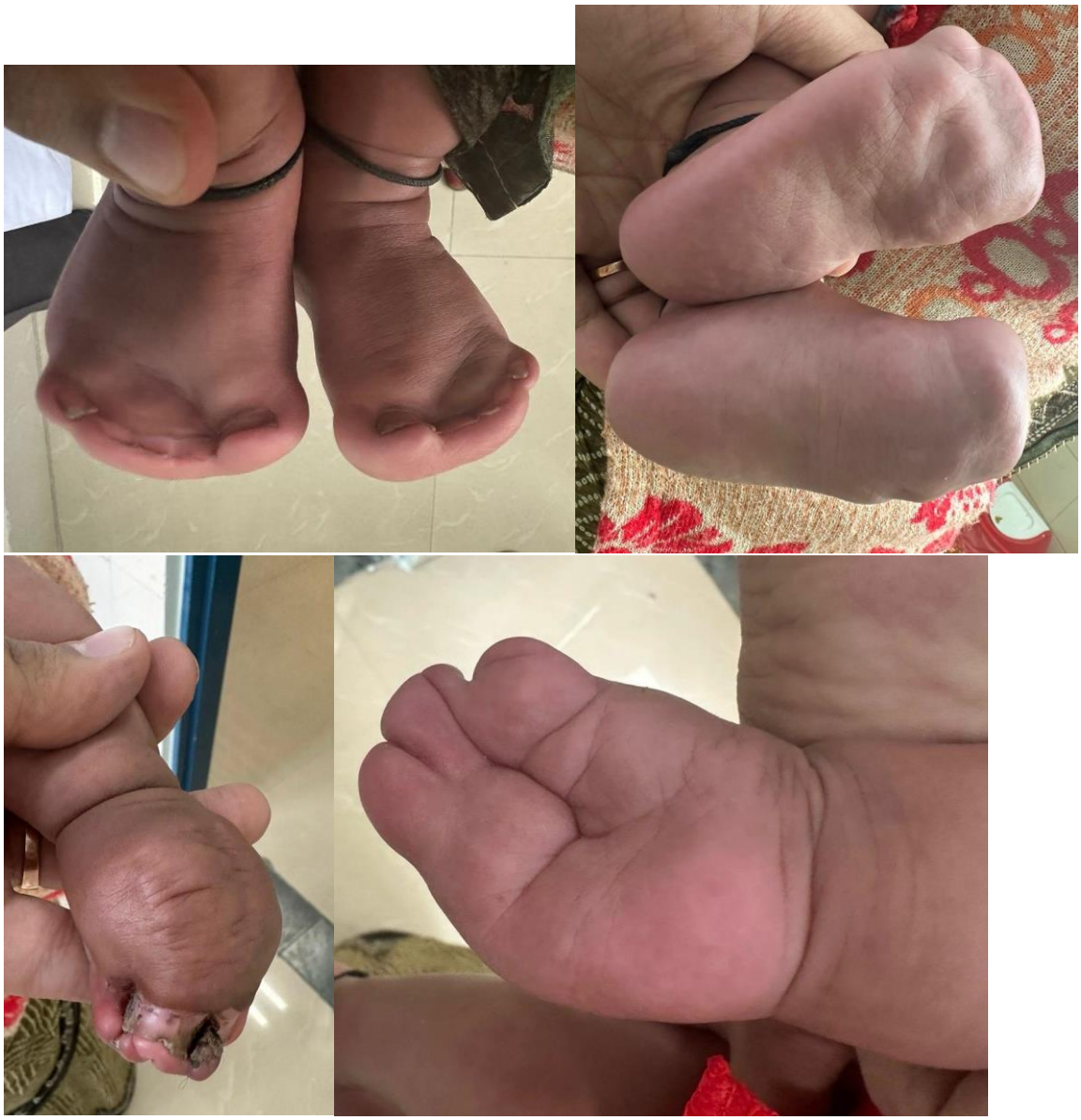


Figure 2: Clinical features of a 1.5-year-old male with Apert Syndrome. (A) Frontal facial view highlighting hypertelorism, shallow orbits, proptosis, turribrachycephaly and (B) Lateral view of the head, demonstrating midfacial hypoplasia, depressed nasal bridge, and parrot-beak nasal appearance (C) Dorsal view of the feet displaying type 3 syndactyly with loss of plantar creases (D) Plantar view showing rosebud feet with complete syndactyly and absent creases, characteristic of Apert phenotype. E) Dorsal view of the hand showing complex, complete syndactyly with a bulbous appearance and nail fusion, characteristic of mitten-hand deformity F) Palmar view of the hand showing complete syndactyly with fusion of digits and a concave, mitten-like appearance—classic of type III syndactyly in Apert Syndrome

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