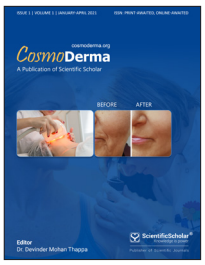
ScientificScholar®
Knowledge is power
Publisher of Scientific Journals

www.cosmoderma.org

CosmoDerma



Review Article

Apert syndrome: A dermatologist's perspective

Nidhi Kamra[1], Ankita Tuknayat[1]

[1]Department of Dermatology, Kalpana Chawla Government Medical College, Karnal, Haryana, India.

***Corresponding author:**
Ankita Tuknayat,
50I3/1 Modern Housing Complex Manimajra,
Chandigarh, India.

anku.tuknayat@gmail.com

Received : 28 October 2021
Accepted : 25 November 2021
Published : 16 December 2021

DOI
10.25259/CSDM_64_2021

Quick Response Code:

ABSTRACT

Apert syndrome is a Type 1 acrocephalosyndactyly syndrome presenting predominantly with craniofacial malformations and syndactyly. It can present with a multitude of clinical features involving any system of the body. A literature search of the PubMed electronic database was performed using the keywords "Apert syndrome" and "dermatology" in the title. The relevant references of the included articles were traced and included. A total of 27 articles appeared, the abstracts of which were screened and reviewed by both the authors independently for inclusion. After carefully analyzing all papers case by case, 21 such cases were retrieved. Cases presenting with other clinical features apart from dermatological features were also reviewed but were not included in the table. A total of about 30 patients of Apert syndrome have been described in dermatological literature, acne being the most common dermatological manifestation. Predominant clinical features in all the cases were brachycephaly due to craniosynostosis and syndactyly of hands and feet. Most of the patients had skeletal, dental, gastrointestinal, genitourinary, respiratory, cardiovascular, and dermatological manifestations in varying proportions. Apert syndrome is a rare entity which can present to a dermatologist. It is, therefore, pertinent to be able to diagnose and recognize the various clinical features of this syndrome to ensure timely management of such patients.

Keywords: Apert, Acrocephaly, Craniosynostoses, Acne

INTRODUCTION

Apert syndrome was first described by Troquart, and later, a case series including nine patients were reported by a French physician, Eugene Apert in 1906 giving the syndrome its name.[1] It is a type 1 acrocephalosyndactyly syndrome having a prevalence of 15.5 per million live births.[2] The characteristic clinical features include acrocephalic (cone shaped) head, premature fusion of coronal sutures, facial dysmorphism, maxillary hypoplasia, and fusion of the digits.[3] There may be associated abnormalities of upper or lower respiratory tract, cardiovascular, genitourinary, and gastrointestinal system. Patients may also present with mental retardation.[3] Presentation with dermatological features like nodulocystic acne is rare.

A review of the PubMed electronic database and an extensive search of literature for systemic involvement in Apert syndrome have been done and an effort is being made to enlist all the clinical manifestations of this rare entity.

MATERIAL AND METHODS

A literature search of the PubMed electronic database was performed using the keywords "Apert syndrome" and "dermatology" in the title. A total of 27 articles appeared, the abstracts

of which were screened and reviewed by both the authors independently for inclusion. Cases presenting with other clinical features apart from dermatological features were also reviewed but were not included in the table.

After carefully analyzing all papers case by case, we were able to retrieve 21 such cases (complete references available on request to the corresponding author), which were re-evaluated, categorized, and outlined as a detailed chronological table. The relevant references of the included articles were also traced and included.

Apert syndrome

Apert syndrome is a type of craniosynostosis syndromes affecting the first branchial arch and is characterized by premature fusion of the sutures along with other systemic anomalies.[4]

Various etiological factors such as maternal viral infection, antenatal drug consumption, and high paternal age have been implicated for this rare syndrome.[5] It is caused due to a missense mutation (substitutions in amino acids Ser252Trp and Pro253Arg) in exon 7 of fibroblast growth factor receptor-2 (FGFR2) on chromosome 10q26. These amino acids are located in linking domains and two isoforms have been studied: (1) Bacterially expressed kinase is expressed on the embryonic skeleton and is responsible for the craniofacial alterations in Apert syndrome; (2) keratinocyte growth factor receptor is expressed in the embryonic epithelium and is responsible for syndactyly. KGF is also involved in differentiation and growth of the hair follicle and it induces increased activity of 5-alpha-reductase Type I in sebaceous glands of acne areas.[6]

Both FGFR2 isoforms (2a and 2b) of this pleiotropic gene are involved in cell proliferation, differentiation, migration, mesenchymal development, and survival in many different contexts including embryonic development, angiogenesis, and tooth morphogenesis. FGFR2b presents in the suprabasal spinous layer of the epidermis and sebocytes binds FGF 7 and 10, has an important role in epidermal differentiation. These FGFR2 mutations in synergy with IGF1 enhance downstream signaling of P13K/Akt pathway, leading to an end-organ hyper-responsiveness to androgen and this androgen-dependent overstimulation causes hyperproliferation and activation of infundibular keratinocytes and sebocytes and early fusion of epiphyses, leading to deformities of skull, hands, and feet. Apert osteoblasts exhibit increased expression of IL-1a and IL-1b.[6]

A total of about 30 patients of Apert syndrome have been described in dermatological literature [Table 1].[4-30] Most of the cases had sporadic mutation. Dermatological features were first described in seven out of nine patients by Solomon *et al*.[5] Predominant clinical features in all the cases were brachycephaly due to craniosynostosis and syndactyly of hands and feet. Most of the patients had multisystemic involvement and had skeletal, dental, gastrointestinal, genitourinary, respiratory, cardiovascular, nervous, otolaryngological, and dermatological manifestations in varying proportions.[8]

Based on this review, we enumerate the various clinical features of Apert syndrome as under:

1. Craniofacial abnormalities
    - Craniosynostosis
    - Turribrachycephaly with a high forehead
    - Asymmetric flat facies
    - Cloverleaf skull appearance
    - Midfacial malformations
        - Pseudoprognathic appearance due to maxillary retroposition
        - Frontal bossing
    - Large and low set ears
    - Trapezoid lips – upper lip is lifted in the midline.
    - Shallow orbits with proptosis
    - Increased digital markings found on interior of skull.
2. Skeletal malformations
    - Symmetrical syndactyly (mitten hand and sock foot/cloven or uncloven hoof)
        - Fusion of the second third and fourth fingers – Most common
        - Severity of the syndactyly scored as: [8]
            - Type I: Thumb and part of fifth finger are separate from syndactylous mass
            - Type II: Little fingers are not separate
            - Type III: Thumb and all fingers are included.
        - Bifurcation of first metatarsal base
    - Lobster claw deformity
    - Short humerus
    - Synostosis of radius and humerus
    - Flat radial head
    - Short or absent neck of scapula
    - Small capitulum
    - Shortened upper limb length relative to body length
    - Fusion of vertebra
    - Deformities of hip joint
    - Diastasis of symphysis pubis
    - Limitation of joint mobility (glenohumeral joint and elbow joint)
    - Ankylosis of elbows, shoulder, and hips
    - Scoliosis
    - Lumbar lordosis.
3. Orodental abnormalities
    - Delayed eruption of teeth – mean dental developmental delay of 0.96 years (range of 0.5–2.9 years)

Table 1: A chronological review of all the cases of Apert syndrome.

Author	Year	Inheritance	Age of the patient	Presenting clinical features	Cutaneous features
Hermann *et al*., Solomon *et al*.[4,5]	1969 and 1970	Sporadic	9 patients 14 y/F 14 y/M 13 y/F 27 y/F 16 y/M 12 y/M 9 y/M 26 y/M 31 y/M	Craniofacial malformations Syndactyly of hands and feet Mental retardation in two patients Conductive hearing loss in three patients Agenesis of corpus callosum in one patient	All seven post-pubertal patients showed moderate-to-severe acne on chest, back, face, arms, and forearms in varying distribution
Sohi and Sohi[15]	1980	Sporadic	1 y/F	Congenital Syndactyly of toes and fingers Acrocephalic skull Flat facies Exophthalmos Hypertelorism Thickened first metacarpal forked at the base Intracranial calcification	Greasy skin
Steffen[16]	1982	Mother had a history of a previous child with anencephaly and missing limb	15 y/M	Craniosynostosis Proptosis Depressed nasal bridge Midface hypoplasia Hypertelorism Syndactyly	Acneiform eruption on the whole skin sparing palms and soles
Robison and Wilms[11]	1989	Sporadic	20 y/M	Facial dysmorphism Syndactyly Brachycephaly	Acneiform eruption over chest, back, and arms
Parker *et al*.[17]	1992	Sporadic	15 y/M	Syndactyly Brachycephaly Facial dysmorphism	Acne on shoulder, chest, upper arms, and forearms
Henderson *et al*.[6]	1995	Sporadic	2 cases 1.16 y/F 2.18 y/F	Syndactyly involving the hands and feet Hypertelorism Midface hypoplasia Proptosis	Severe cystic acne involving the face, back, chest, arms, and forearms
Downs *et al*.[18]	1999	Sporadic	11 y/M	Craniofacial malformations Choanal atresia Syndactyly (atypical form – only soft-tissue fusion) Cleft palate Mild mental retardation Reduced shoulder and elbow movement Obstructive sleep apnea	Pustular acne over face, upper torso, arms, and thighs Greasy skin and hair
Gilaberte *et al*.[19]	2003	Sporadic	13 y/M	Craniosynostosis Syndactyly of hands and feet	Pustular and cystic acne on face, trunk, arms, and thighs
Cuerda *et al*.[7]	2003	Sporadic	12 y/M	Craniosynostosis Syndactyly of hands and feet Epilepsy	Cysts and pustular lesions located on the arms, upper chest, and back, without involvement of the face, as well as hyperhidrosis of the palms and soles

(Contd..)

Table 1: *(Continued)*

Author	Year	Inheritance	Age of the patient	Presenting clinical features	Cutaneous features
Mukhopadhyay *et al.*[20]	2004	Sporadic	2 m/F	Facial dysmorphism Low posterior hairline High-arched palate Syndactyly Hydrocephalus Atrophy of frontal and parietal lobes Bifurcation of first metatarsal base Epigastric hernia	Acneiform lesions on the nose
Verma and Draznin[21]	2005	Sporadic	10 y/M	Symmetric syndactyly of all digits of the hands and feet Midface hypoplasia Exophthalmia ocular Hypertelorism Cleft palate	Hyperhidrosis of feet Synonychia Onychomycosis
Benjamin *et al.*[22]	2005	Autosomal dominant	Twins 13 y/M	Facial dysmorphism Syndactyly Brachycephaly Twin A – aortic stenosis, asthma, ventricular septal defect Twin B – omphalocele, coarctation of aorta	Twin A – Stage 4 acne Twin B – Stage 3 acne
Hsieh and Ho[13]	2005	Sporadic	15 y/F	Midface hypoplasia Brachycephaly Syndactyly	Severe acne on face, chest, back, abdomen, and forearms
Freiman *et al.*[23]	2006	Sporadic	14 y/M	Brachycephalic Broad nose with bulbous tip Hypertelorism. Bilateral symmetrical syndactyly of both his hands and feet	Hyperkeratosis on the lateral plantar aspects mild acneiform papules on the face and upper extremities
Tiwari *et al.*[24]	2007	Sporadic	20 y/F	Symmetrical syndactyly of all the digits of the hands and feet Progressive loss of vision in the right eye Short stature Midface hypoplasia Exophthalmia of the right eye Corneal opacity in the right eye Ocular hypertelorism Subnormal intelligence Septo-optic dysplasia Corneal opacity Phthisis bulbi Agenesis of the septum pellucidum	Synonychia Onychomycosis
DeGiovanni *et al.*[25]	2007	sporadic	13 y/F	Dysmorphic facies Brachycephaly Exophthalmos Depressed nasal septum Symmetrical syndactyly of the index-middle fingers and all toes Physical and developmental delay CT head scan showed Dandy-Walker variant	Moderate pustular acne was seen on the forearms and back of the trunk
De *et al.*[26]	2008	Sporadic	8 m/M	Syndactyly of all four limbs Brachycephaly Frontal bossing Midface hypoplasia, depressed nasal bridge Upward slanting of the eyes Low-set ears Growth and mental retardation	No

(Contd..)

Table 1: *(Continued)*

Author	Year	Inheritance	Age of the patient	Presenting clinical features	Cutaneous features
Dolenc-Voljč and Finžgar-Perme[27]	2008	Sporadic	14 y/M	Brachycephaly Syndactyly Facial dysmorphism	On initial presentation, numerous comedones, papules, pustules, and nodular acne lesions were seen on the face, neck, chest, and back, extending to the upper arms, forearms, thighs, and shanks
Paradisi *et al.*[28]	2011	Sporadic	15 y/M	Brachycephaly Hypertelorism Mandibular prognathism Parrot beak nose Cutaneous and osseous syndactyly of hands	Papulopustular and nodular lesions on the face
Bissacotti *et al.*[29]	2016	Sporadic	15 y/F	Acrocephaly hypertelorism proptosis Strabismus Interrupted eyebrows Maxillary hypoplasia Mandibular overjet Malocclusion Misalignment and crowding of the teeth Symmetric syndactyly of the hands and feet Scoliosis	Acne Palmoplantar hyperhidrosis Plantar hyperkeratosis Nail dystrophy
Langenderfer *et al.*[30]	2019	Sporadic	37 y/M	Craniosynostosis Neurogenic bladder Bilateral hearing loss Migraines Flat forehead Midface Syndactyly Hypertelorism Neurogenic bladder	Inflammatory and nodulocystic acne involving the face, chest, and back

- Crowding of teeth within the alveolus
- Supernumerary teeth
- Congenitally missing teeth
- Malocclusion
- Thick gingiva
- Shovel-shaped incisors[9]
- Bilateral crossbite
- Mandibular overjet
- Midline deviation
- Narrow palate
- Cleft palate or bifid uvula – 75% of the cases
- Reduction in the size of the maxilla
- Anterior open bite of the maxilla
- Speech and articulation defects/hyper-resonant due to malocclusion[10]
- Arched hard palate with bilateral swellings of the palatine processes, resulting in a pseudocleft in the midline.
- Low postured and protruded tongue.

4. Dermatological
   - Broad, short fused nails (synonychia) with micronychia
   - Brittle nails
   - Acne – starting from the age of 9–12 years
   - Pigmentary dilution of skin and hair
   - Hyperhidrosis
   - Oculocutaneous albinism
   - Interrupted eyebrows
   - Forehead wrinkling
   - Paronychial infections
   - Skin dimpling over the knuckles, shoulders, and elbows
   - Lateral plantar hyperkeratosis.[28]
5. Ophthalmological
   - Pigmentary dilution of eyes
   - Hypertelorism
   - Divergent squint
   - Optic atrophy
   - Phthisis bulbi
   - Optic nerve hypoplasia
   - Keratoconus
   - Hyperopic eyes
   - Proptosis
   - Errors of refraction

- Exposure keratitis
- Blindness.

6. Otolaryngological anomalies
   - Small nose (occasionally parrot beak like)
   - Choanal atresia
   - Obstructive sleep apnea
   - Conductive hearing loss.
7. Cardiovascular anomalies (10%)
   - Atrial and ventricular septal defects
   - Overriding aorta
   - Endocardial fibroelastosis.
8. Renal anomalies
   - Hydronephrosis
   - Polycystic kidney
   - Hypernephrosis.
9. Gastrointestinal anomalies
   - Esophageal atresia
   - Pyloric stenosis
   - Ectopic anus
   - Hernia.
10. Respiratory
    - Pulmonary aplasia
    - Atrophy of pulmonary arteries
    - Anomalies of tracheal cartilage
    - Pulmonary stenosis.
11. Genitourinary anomalies (9.6%)
    - Bicornuate uterus
    - Neurogenic bladder
    - Recurrent urinary tract infections.
12. Central nervous system anomalies
    - Agenesis of corpus callosum
    - Megalencephaly
    - Gyral abnormalities
    - Encephalocele
    - Pyramidal tract abnormalities
    - Hypoplasia of cerebral white matter
    - Heterotopic gray matter
    - Hypoplasia or absence of the septum pellucidum
    - Hippocampal hypoplasia or dysplasia
    - Ventriculomegaly
    - Cavum vergae.
13. Psychological problems
    - Mental retardation
    - Antisocial behavior.

Among the dermatological manifestations, acne is the most prominent feature. It usually starts at the age of 9–12 years.[11] The acne in this syndrome is severe, inflammatory or comedonal, located at face, chest, back, as well as unusual sites such as arms, forearms, buttocks, and thighs and they are recalcitrant to treatment. Munro's acne nevus, a mosaic cutaneous manifestation of Apert syndrome, has also been studied and it is characterized by sharply bordered acneiform lesions along the lines of Blaschko.[12]

The pathogenesis of acne is similar, that is, involving the FGFR2 and causing sebaceous hyperplasia due to end-organ hypersensitivity to androgen.[12] Various treatment options for acne have been tried including multiple oral and topical antibiotics and azelaic acid. It has been observed that isotretinoin in a dose of 1–2 mg/kg/day has the maximum benefit in such patients as it is involved in downregulating FGFR2 signaling. Recently, oral contraceptive pills have also been tried in the treatment of acne in Apert syndrome.[13] Isotretinoin is usually started at a higher dose in such patients and majority of patients remain clear of acne for months. However, some relapses may occur, requiring repeated dosing. It carries the risk of serious side effects such as hyperostosis and pseudotumor cerebri, thus risk-benefit ratio should be assessed in treating such patients.

Other craniosynostosis syndromes involving the same FGFR 2 gene may be considered in the differential diagnosis of Apert syndrome. Almost 70 such syndromes have been studied including Crouzon syndrome, Pfeiffer syndrome, and JacksonWeiss syndrome. Crouzon syndrome has normal hands and feet as well as normal intelligence. When fusions are present, C5–C6 involvement in the Apert syndrome and C2–C3 involvement in Crouzon syndrome separate the two conditions in most cases. Acanthosis nigricans is a dermatologic association with Crouzon syndrome.[3]

The presence of broad and medially deviated thumbs and halluces in association with cutaneous syndactyly differentiates Pfeiffer syndrome from Apert syndrome. Cutaneous hypopigmentation can also be associated with Pfeiffer syndrome.[4]

Other syndromes presenting with dysmorphic features and bony abnormalities like Carpenter syndrome can be kept as a differential diagnosis.[4] This Ras-related protein (RAB23) craniosynostosis characteristically has brachydactyly, syndactyly, aplasia, or hypoplasia of the hands and/or polydactyly of the feet. It is characterized by hypogenitalism or obesity which is not a feature of Apert syndrome.

Saethre-Chotzen syndrome, also known as acrocephalosyndactyly Type 3, has craniosynsostosis, ptosis, partial syndactyly, and hearing loss but most patients have normal intelligence. It has a mutation in TWIST1 gene on chromosome 7p21.[14]

Patients with Apert syndrome require multidisciplinary approach to management. Neurosurgeons, plastic surgeons, otorhinolaryngologists, orthodontists, ophthalmologists, radiologists, geneticists, pediatricians, and dermatologists must all work in concert to care for such patients. Early surgical intervention is imperative for optimal outcomes. Subsequent treatment should be tailored to each individual patient's needs.

CONCLUSION

Apert syndrome is a rare entity which can present to a dermatologist. It is, therefore, pertinent to be able to diagnose and recognize the various clinical features of this syndrome to ensure timely management of such patients.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Apert ME. De l'acrocephalosynactylie. Bull Mem Soc Med Hosp Paris 1906;23:1510.
2. Cohen MM, Kreiborg S, Lammer EJ, Cordero JF, Mastroiacovo P, Erickson JD, *et al*. Birth prevalence study of the Apert syndrome. Am J Med Genet 1992;42:655-9.
3. Katzen JT, McCarthy JG. Syndromes involving craniosynostosis and midface hypoplasia. Otolaryngol Clin North Am 2000;33:1257-84.
4. Hermann J, Pallister PD, Opitz JM. Craniosynostosis and craniosynostosis syndromes. Rocky Mt Med J 1969;66:45-56.
5. Solomon LM, Fretzin D, Pruzansky S. Pilosebaceous abnormalities in Apert's syndrome. Arch Dermatol 1970;102:381-5.
6. Henderson C, Knaggs H, Clark A, Highet AS, Cunliffe WJ. Apert's syndrome and androgen receptor staining of the basal cells of sebaceous glands. Br J Dermatol 1995;132:139-43.
7. Cuerda E, Pozo JD, Rodrìguez-Lozano J, Peña-Penabad C, Fonseca E. Acne in Apert's syndrome: Treatment with isotretinoin. J Dermatol Treat 2003;14:43-5.
8. Wilkie AO, Wall SA. Craniosynostosis-novel insights into the pathogenesis and treatment. Curr Opin Neurol 1996;9:146-52.
9. Taksande A, Vilhekar K, Khangare S. Apert syndrome: A rare presentation. J Indian Acad Clin Med 2007;8:245-6.
10. Bhatia PV, Patel PS, Jani YV, Soni NC. Apert's syndrome: Report of a rare case. J Oral Maxillofac Pathol 2013;17:294-7.
11. Robison D, Wilms NA. Successful treatment of the acne of Apert syndrome with isotretinoin. J Am Acad Dermatol 1989;21:315-6.
12. Melnik BC, Schmitz G, Zouboulis CC. Anti-acne agents attenuate FGFR2 signal transduction in acne. J Invest Dermatol 2009;129:1868-77.
13. Hsieh T, Ho N. Resolution of acne following therapy with an oral contraceptive in a patient with Apert syndrome. J Am Acad Dermatol 2005;53:173-4.
14. Hollway GE, Suthers GK, Haan EA, Thompson E, David DJ, Gecz J, *et al*. Mutation detection in FGFR2 craniosynostosis syndromes. Hum Genet 1997;99:251-5.
15. Sohi BK, Sohi AS. Apert's syndrome. Indian J Dermatol Venereol Leprol 1980;46:169-72.
16. Steffen C. Acneform eruption in Apert's syndrome. Arch Dermatol 1982;118:206-8.
17. Parker TL, Roth JG, Esterly NB. Isotretinoin for acne in Apert syndrome. Pediatr Dermatol 1992;9:298-300.
18. Downs AM, Condon CA, Tan R. Isotretinoin therapy for antibiotic-refractory acne in Apert's syndrome. Clin Exp Dermatol 1999;24:461-3.
19. Gilaberte M, Puig L, Alomar A. Isotretinoin treatment of acne in a patient with apert syndrome. Pediatr Dermatol 2003;20:443-6.
20. Mukhopadhyay AK, Mukherjee D. Aper's syndrome. Indian J Dermatol Venereol Leprol 2004;70:105-7.
21. Verma SH, Draznin M. Apert syndrome. Dermatol Online J 2002;11:15.
22. Benjamin LT, Trowers AB, Schachner LA. Successful acne management in Apert syndrome twins. Pediatr Dermatol 2005;22:561-5.
23. Freiman A, Tessler O, Barankin B. Apert syndrome. Int J Dermatol 2006;45:1341-3.
24. Tiwari A, Agrawal A, Pratap A, Lakshmi R, Narad R. Apert syndrome with septum pellucidum agenesis. Singapore Med J 2007;48:62-5.
25. DeGiovanni CV, Jong C, Woollons A. What syndrome is this? Apert syndrome. Pediatr Dermatol 2007;24:186-8.
26. De D, Narang T, Kanwar AJ, Dogra S. Brachycephaly and syndactyly: Apert's syndrome. Indian J Dermatol Venereol Leprol 2008;74:395-6.
27. Dolenc-Voljč M, Finžgar-Perme M. Successful isotretinoin treatment of acne in a patient with apert syndrome. Acta Derm Venereol 2008;88:534-5.
28. Paradisi A, Ghitti F, Capizzi R, Fossati B, Amerio PL, Guerriero C. Acne treatment with isotretinoin in a patient with Apert syndrome. Eur J Dermatol 2011;21:611-2.
29. Steglich EM, Steglich RB, Melo MM, de Almeida HL Jr. Extensive acne in Apert syndrome. Int J Dermatol 2016;55:596-8.
30. Langenderfer L, Giesey R, Ezaldein H, Delost GR. Acne and craniofacial defects. JAAD Case Rep 2019;5:495-7.

How to cite this article: Kamra N, Tuknayat A. Apert syndrome: A dermatologist's perspective. CosmoDerma 2021;1:66.