

Case report

Apert syndrome

Anatoli Freiman, MD, Oren Tessler, MD, and Benjamin Barankin, MD

From the Division of Dermatology, McGill University, Montreal, Canada, and Division of Dermatology, University of Alberta, Edmonton, Canada

Correspondence

Anatoli Freiman, MD
Division of Dermatology
McGill University Health Center
3550 Jeanne-Mance St., Suite 2506
Montreal, Québec, H2 × 3P7 Canada
E-mail: anatoli.freiman@sympatico.ca

Abstract

Apert syndrome or acrocephalosyndactyly is a rare autosomal dominant malformation syndrome characterized by craniosynostosis, symmetric severe syndactyly, and a variety of abnormalities of the skin, skeleton, brain, and visceral organs. A case of Apert syndrome and the clinical and specific cutaneous manifestations of this condition are reviewed.

Case Report

A 14-year-old boy presented to the dermatology clinic with a four-year history of acne refractory to therapy. The condition began in the form of oily skin, followed by the appearance of papules and pustules on the face and upper trunk. Treatment with different regimens, including topical benzoyl peroxide, tretinoin, and oral tetracycline did not result in any significant improvement.

The patient was born at term of an uncomplicated pregnancy, without significant medical history in the family. At birth, the infant was remarkable for craniofacial deformities including depressed fontanels, a palpable coronal suture, and a brachycephalic skull. Symmetric osseous fusion of the 2nd to 5th digits of his hands and feet was present. The child showed mild motor and cognitive developmental delay and hyperhidrosis.

On examination, the boy's skull appeared brachycephalic with a flat occiput, a short broad nose with bulbous tip, and slight hypertelorism. Bilateral symmetrical syndactyly of both his hands and feet with hyperkeratosis on the lateral plantar aspects was noted (Fig. 1). Mild acneiform papules were present on the face and upper extremities, and on close examination, the patient's skin was found to be oily with uniformly dilated hyperkeratotic follicles (Fig. 2). The constellation of the clinical features of this case was compatible with the diagnosis of Apert syndrome.

Discussion

Apert syndrome or acrocephalosyndactyly is a rare malformation syndrome first described by Wheaton in 1894 and



Figure 1 Bilateral symmetrical syndactyly of the feet

later by Apert in 1906.¹ It occurs with a reported birth prevalence of 1/65 000.² The hallmarks of the syndrome include craniosynostosis (abnormal development and premature fusion of the cranial sutures), symmetric severe syndactyly (cutaneous and bony fusion of the digits), and a variety of abnormalities of the skin, skeleton, brain, and visceral organs.

The condition results from a specific missense mutation in the gene-encoding fibroblast growth factor receptor-2 (FGFR-2), mapped to 10q26 chromosome. This pleiotropic gene is involved in the complex intercellular signaling network that controls cell proliferation, differentiation, migration, and survival in many different contexts, including embryonic development, angiogenesis, and malignancy.³ Mutations of the FGFR-2 gene have also been associated with several other

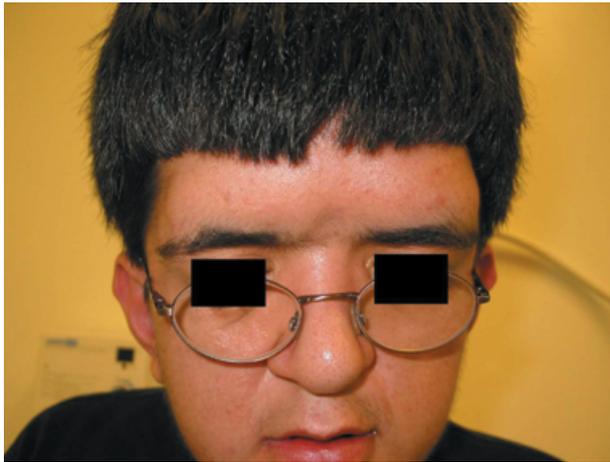


Figure 2 Oily skin with mild acne and a midline skull defect above the patient's nose

craniosynostosis malformation syndromes, including Crouzon, Jackson–Weiss, Pfeiffer, and Beare–Stevenson cutis gyrata syndromes.⁴ Most cases of Apert syndrome are sporadic, while autosomal dominant transmission and germinal mosaicism have also been reported.⁵ The paternal origin of new mutations, specifically related to age effect, has been elucidated.⁶

Premature fusion of cranial sutures, most commonly of the coronal suture, is observed in all patients with Apert syndrome. Antero–posterior shortening of the cranial base leads to acrocephaly or brachycephaly. Other characteristic craniofacial abnormalities include prominent forehead with skin wrinkling, broad cranium, and a flat occiput. Hypertelorism, proptosis, and strabismus are often present due to shortening of the bony orbit.⁷ Additional craniofacial features include a short, broad nose with a bulbous tip, micrognathia, and a cleft palate.⁸ Symmetric syndactyly of the hands and feet is another

universal finding in patients with Apert syndrome. Central nervous system abnormalities include defects of the corpus callosum and limbic structures, ventriculomegaly, and progressive hydrocephalus. A significant number of patients function at an intellectual level two standard deviations below the mean.⁹ Cardiovascular and genitourinary defects occur in 10% and 9.6% of patients with the syndrome, respectively.¹⁰

An overview of cutaneous findings associated with craniosynostoses caused by *FGFR2* mutations is presented in Table 1. A number of cutaneous manifestations are characteristic of Apert syndrome, including hyperhidrosis, interrupted eyebrows (thought to be caused by underlying bony defects), forehead wrinkling, and skin dimpling over knuckles, shoulders, and elbows.¹¹ As a result of progressive osseous fusion of the tarsal and metatarsal bones, transfer of weight bearing to the mid- and lateral plantar regions occurs in most patients, leading to lateral plantar hyperkeratosis. Moreover, patients may show cutaneous and ocular hypopigmentation as a result of the failure of melanoblast migration *in utero*.¹²

Acneiform lesions in patients with Apert syndrome were first described by Solomon *et al.* in 1971¹³ and subsequently elucidated by a number of authors. Oily skin is noted at adolescence, with subsequent appearance of follicular acneiform papules. In addition to the involvement of the face and upper trunk, and in contrast to classic acne, the distribution of lesions is more diffuse, often involving the forearms, buttocks, and thighs.^{8,13} Acneiform lesions have also been reported to occur in a nevoid distribution pattern, attributed to epidermal mosaicism in patients with somatic mutation of *FGFR-2*.¹⁴ The etiology of these acneiform lesions remains controversial. Solomon hypothesized that end-organ androgen metabolism defects may lead to sebaceous gland abnormalities in patients with Apert syndrome,¹³ while Steffen suggested that structural malformations of the pilosebaceous apparatus itself may be the cause of acne.⁷ *FGFR-2* might play a role in regulating

Syndrome	Cutaneous manifestations
Apert syndrome ¹¹	Resistant acne Hyperhidrosis Interrupted eyebrows Excessive forehead wrinkling Lateral plantar hyperkeratosis Skin dimpling over joints Oculocutaneous hypopigmentation
Crouzon syndrome	Acanthosis nigricans (5%)
Jackson–Weiss syndrome	Low anterior hairline
Pfeiffer syndrome	Cutaneous hypopigmentation (10%) Broadening of thumbs and great toes Partial soft tissue syndactyly of the hands and feet
Beare–Stevenson cutis gyrata	Cutis gyrata Deep palmoplantar creases Acanthosis nigricans (hands and feet) Acrochordons

Table 1 Cutaneous manifestations of craniosynostoses caused by *FGFR2* mutations

androgen sensitivity of the folliculo-sebaceous unit.¹⁴ No increase in circulating androgens, nor in the number of sebaceous gland androgen receptors have been documented so far. Acneiform lesions in patients with Apert syndrome tend to be unusually resistant to pharmacologic therapy. Evidence from several case reports suggests that oral isotretinoin may be most beneficial.¹⁵⁻¹⁷

Recently, resolution of acne following oral contraceptive therapy has been reported in a female patient with Apert syndrome.¹⁸

References

- 1 Apert M. De l'acrocephalosyndactylie. *Bull Mem Soc Med Hop Paris* 1906; 23: 1310-1313.
- 2 Cohen MM Jr, Kreiborg S, Lammer EJ, *et al*. Birth prevalence study of the Apert syndrome. *Am J Med Genet* 1992; 42: 655-659.
- 3 Wilkie AO, Slaney SF, Oldridge M, *et al*. Apert syndrome results from localized mutations of FGFR2 and is allelic with Crouzon syndrome. *Nat Genet* 1995; 9: 165-172.
- 4 Hollway GE, Suthers GK, Haan EA, *et al*. Mutation detection in FGFR2 craniosynostosis syndromes. *Hum Genet* 1997; 99: 251-255.
- 5 Allanson JE. Germinal mosaicism in Apert syndrome. *Clin Genet* 1986; 29: 429-433.
- 6 Moloney DM, Slaney SF, Oldridge M, *et al*. Exclusive paternal origin of new mutations in Apert syndrome. *Nat Genet* 1996; 13: 48-53.
- 7 Steffen C. Acneiform eruption in Apert syndrome. Acrocephalosyndactyly. *Arch Dermatol* 1982; 118: 206-208.
- 8 McNaughton PZ, Rodman OG. Apert syndrome. *Cutis* 1980; 25: 538-540.
- 9 Cohen MM Jr, Kreiborg S. The central nervous system in the Apert syndrome. *Am J Med Genet* 1990; 35: 36-45.
- 10 Cohen MM Jr, Kreiborg S. Visceral anomalies in the Apert syndrome. *Am J Med Genet* 1993; 45: 758-760.
- 11 Cohen MM Jr, Kreiborg S. Cutaneous manifestations of Apert syndrome. *Am J Med Genet* 1995; 58: 94-96.
- 12 Margolis S, Siegel IM, Choy A, *et al*. Depigmentation of hair, skin, and eyes associated with the Apert syndrome. *Birth Defects Orig Artic Series* 1978; 14: 341-360.
- 13 Solomon LM, Cohen MM Jr, Pruzansky S. Pilosebaceous abnormalities in Apert-type acrocephalosyndactyly. *Birth Defects Orig Artic Series* 1971; 7: 193-195.
- 14 Munro CS, Wilkie AO. Epidermal mosaicism producing localised acne: somatic mutation in FGFR2. *Lancet* 1998; 352: 704-705.
- 15 Campanati A, Marconi B, Penna L, *et al*. Pronounced and early acne in Apert syndrome: a case successfully treated with oral isotretinoin. *Eur J Dermatol* 2002; 12: 496-498.
- 16 Cuerda E, del Pozo J, Rodriguez-Lozano J, *et al*. Acne in Apert syndrome: treatment with isotretinoin. *J Dermatolog Treat* 2003; 14: 43-45.
- 17 Gilaberte M, Puig L, Alomar A. Isotretinoin treatment of acne in a patient with Apert syndrome. *Pediatr Dermatol* 2003; 20: 443-446.
- 18 Hsieh T, Ho N. Resolution of acne following therapy with an oral contraceptive in a patient with Apert syndrome. *J Am Dermatol* 2005; 53(1): 173-174.