

## Successful Isotretinoin Treatment of Acne in a Patient with Apert Syndrome

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Sir,

Apert syndrome (acrocephalosyndactyly type I), first described in 1906 by the French physician Eugène Apert, is a rare autosomal dominant congenital disorder characterized by the premature obliteration of the craniofacial sutures and syndactyly of the hands and feet (1). In most patients it is caused by a localized mutation in the gene encoding for the fibroblast growth factor receptor (FGFR2), which is responsible for the development of embryonic skeleton, epithelial structures and connective tissue (2). An incidence of 1:160,000 live births was found in a British study (1), but a higher birth prevalence (1:65,000 or 15.5 per million) was estimated several decades later (3). More than 98% of cases are caused by a new mutation, which is of paternal origin, and association with older paternal age has been implicated.

The irregular obliteration of the cranial sutures results in different craniofacial deformities, hypertelorism, dental and palatal abnormalities and a tendency towards proptosis of the eyes (1, 4). Several other skeletal deformities as well as cardiovascular, urogenital, gastrointestinal, respiratory and skin abnormalities have been described. Increased intracranial pressure may lead to hydrocephalus, abnormal brain development, and different levels of mental retardation, blindness and death.

Early neurosurgical intervention is therefore essential for a good prognosis in these patients (4).

Since 1970 Apert syndrome has been discussed also in dermatological literature; Solomon et al. (5) were the first to describe pilosebaceous abnormalities in these patients. Early appearance of widespread and severe acne, resistant to conventional therapies, is a common feature in these patients. We describe here a patient with Apert syndrome and severe acne who had a good response to treatment with isotretinoin, and discuss previous reports of the use of oral isotretinoin in this syndrome.

### CASE REPORT

A 14-year-old boy with Apert syndrome was referred to our department for treatment of severe, disseminated and refractory acne. The patient had the classical facial and acral deformities of Apert syndrome. In early childhood, he underwent a neurosurgical operation that successfully opened the prematurely closed cranial sutures.

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 (Fig. 1a). Acne had been present for 4 years. Previous treatment with oral tetracycline given for 2 months, and topical clindamycin and adapalene had proved ineffective.

Isotretinoin was instituted at a daily dose of 30 mg (0.5 mg/kg/day). After 2 months of this therapy, clearing of acne was



Fig. 1. (a) Acne on the face, chest and upper arms prior to isotretinoin treatment. Typical face of Apert syndrome. (b) Improvement after isotretinoin treatment.

perceptible on the face, while resolution on the trunk and extremities was slower. After 11 weeks of treatment, the dose was reduced to 20 mg/day (0.3 mg/kg/day), and this was administered for the next 30 weeks. The total dose of isotretinoin was 112 mg/kg. In conjunction with the systemic treatment, topical therapy with azelaic acid cream was applied to the face and trunk. On discontinuation of the systemic treatment, very good regression of acne was evident in all affected areas (Fig. 1b). Numerous residual atrophic and hypertrophic scars were present on the trunk and arms.

Routine laboratory examinations, liver function tests and lipid studies were regularly performed, and the values remained within normal limits throughout the treatment period. The drug was well tolerated, skin dryness being the only adverse effect. The patient was co-operative and mentally well adjusted. He has remained in good remission for 2 years. Mild residual papular acne is well controlled with topical adapalene.

## DISCUSSION

Acne in Apert syndrome appears at puberty, usually between 9 and 12 years of age. Unusual sites such as the forearms and thighs are often involved (4, 5). Forearm acne is believed to occur only in the most severe cases (5). The pathogenesis of acne in this syndrome is not adequately explained. Formerly, acne in these patients was perceived as a congenital abnormality of pilosebaceous units and not as true acne vulgaris (6). Later it was interpreted as a peculiar presentation of acne vulgaris (7, 8). Studies using staining of the basal cells of sebaceous glands (9) and morphological, ultrastructural and immunohistochemical techniques (7) support the view that acne in Apert syndrome results from the increased sensitivity of sebaceous glands to normal levels of circulating androgens. A hyper-response to androgens, perhaps mediated by keratinocyte growth factor receptors, may also explain the premature epiphyseal fusion in Apert syndrome (8, 10).

Acne in Apert syndrome is often refractory to topical and oral antibiotics (9–11). Several reports have indicated that isotretinoin is the treatment of choice for acne in these patients (7–14). Different dosage regimens have been used so far, and prolonged treatment or repeated courses of the drug have occasionally been necessary (9, 14). In some patients the daily dose reached 1 mg/kg (10, 11) or even 1.5 mg/kg (9). In others good results were achieved with a daily dose of approximately 0.8 mg/kg (7, 12, 13). The total dose of isotretinoin given to patients has varied from 94 to 140 mg/kg (10, 12, 13). In many reports, the total dose is not stated.

The daily dose of isotretinoin used to treat severe and disseminated acne in our patient was comparatively low, but the treatment period was somewhat longer than in the above reports. Some authors believe that severe acne in patients with Apert syndrome should be treated aggressively from the outset (9). However, our experience

does not justify this approach. The total dose of isotretinoin given to our patient was also comparatively low. A total dose of at least 120 mg/kg is thought to be necessary in order to minimize post-therapy relapse, but the treatment must be adjusted depending on the clinical efficacy of the drug in each patient. Lower daily doses of isotretinoin have been recommended (15). The use of lower doses is advisable especially for teenage patients with Apert syndrome, in whom the risk/benefit ratio of the treatment should be evaluated carefully (13).

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