CLINICAL ARTICLES

Cleft Lip and Palate Repair in Hay-Wells/Ankyloblepharon-Ectodermal Dysplasia-Clefting Syndrome

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Hay-Wells/ankyloblepharon-ectodermal dysplasia-clefting syndrome is a rare autosomal dominant disorder characterized by ankyloblepharon, ectodermal dysplasia, and cleft lip and/or cleft palate. Mutations in the p63 gene recently have been shown to be etiologic in the majority of cases of ankyloblepharon-ectodermal dysplasia-clefting syndrome. To date, there have been no reports to document wound healing after cleft lip and/or palate repair in ankyloblepharon-ectodermal dysplasia-clefting patients. We describe two patients with ankyloblepharon-ectodermal dysplasia-clefting syndrome and provide a review of the literature. There have been no reported instances of wound healing complications in affected patients. Seventeen percent (3/18) of reported patients required revisions or repair of oronasal fistulae. Cleft lip and palate repair can be performed safely in patients with Hay-Wells syndrome.

KEY WORDS: *AEC, cleft lip, cleft palate, ectodermal dysplasia, Hay-Wells, p63, wound healing*

Hay-Wells/ankyloblepharon-ectodermal dysplasia-clefting (AEC) syndrome (OMIM 106260) is a rare autosomal dominant disorder characterized by ankyloblepharon, ectodermal dysplasia, and cleft palate and/or cleft lip. Other features of the disorder include alopecia, erosive scalp dermatitis, onychodystrophy, hypodontia, hypohidrosis, and maxillary hypoplasia. The syndrome was first described Hay and Wells (1976) in a series of seven patients from four families. Since that time, 40 other cases have been reported in the English literature (Spiegel and Colton, 1985; Shwayder et al., 1986; Greene et al., 1987; Fosko et al., 1992; Weiss et al., 1992; Seres-Santamaria et al., 1993; Vanderhooft et al., 1993; Cambiaghi et al., 1994; Satoh et al., 1994; Mancini and Paller, 1997; Zenteno et al., 1999; Bertola et al., 2000; McGrath et al., 2001; Drut et al., 2002; Tsutsui et al., 2003; Lodha and Ng, 2004; Sahin et al., 2004; Payne et al., 2005; Propst et al., 2005; Steele et al., 2005; Kulkarni et al., 2006). Ankyloblepharon in affected patients usually is limited to small bands of vascularized connective tissue spanning the eyelids (ankyloblepharon filiforme adnatum), and such is the classical feature that distinguishes AEC syndrome from two other disorders that also present with ectodermal dysplasia and cleft palate and/or cleft lip. Ectrodactyly-ectodermal dysplasia-clefting syndrome (EEC syndrome; OMIM 129900) is characterized by the triad of ectrodactyly, ectodermal dysplasia, and cleft palate and/or cleft lip, whereas Rapp-Hodgkin syndrome (RHS; OMIM 129400) is distinguished by ectodermal dysplasia and cleft palate and/or cleft lip, without ectrodactyly or ankyloblepharon.

Recently, advancements in molecular diagnostic medicine have confirmed the long-recognized clinical parallels among these syndromes. Mutations in the p63 gene, a p53 family member important in limb, craniofacial, and epithelial development (Mills et al., 1999; Yang et al., 1999), have been shown to cause all three disorders (Celli et al., 1999; McGrath et al., 2001; Dianzani et al., 2003). The p63 gene also is known to play important roles in epithelial maintenance, wound healing, and muscle repair (Noszczyk and Majewski, 2001; Koster and Roop, 2004; Bamberger et al., 2005). The p63 mutations present in Hay-Wells patients are thought to interfere with normal keratinocyte proliferation, differentiation, and survival and result in the observed skin manifestations of the disorder

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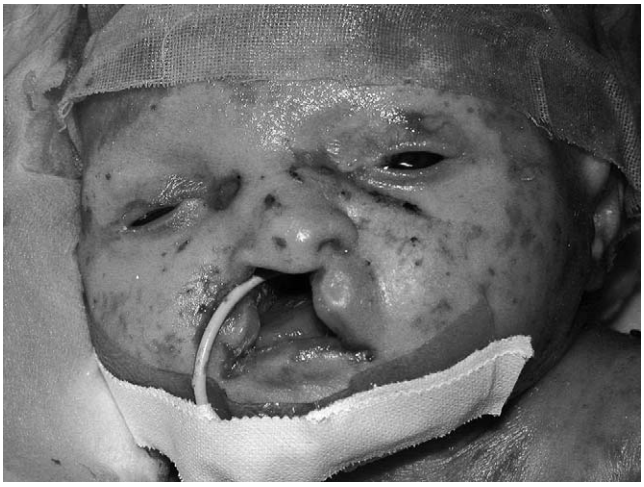

FIGURE 1 Wide unilateral cleft lip in patient A. Denuded skin of the face and right-sided ankyloblepharon are also apparent.

(Fomenkov et al., 2003; Beretta et al., 2005; Huang et al., 2005; Lo Iacono et al., 2006; Testoni and Mantovani, 2006). It is unknown, however, if these mutations impair the wound healing process. Herein we report on two patients with Hay-Wells syndrome who presented to our institution and who underwent cleft lip and/or cleft palate repair.

Case Reports

Case A

A full-term female infant presented to the plastic surgery service on day 13 of life with a wide right unilateral cleft lip and palate, ankyloblepharon of the right eyelid, onychodystrophy, syndactyly of the fourth and fifth toes bilaterally, and widespread erosions and pustular lesions on the extremities and scalp (Fig. 1). Ulcerations of the buccal mucosa also were present. Pregnancy was complicated by maternal hypertension but required no medical intervention. At delivery, 80% of the infant's total body surface area was denuded. Further evaluation revealed bilateral lacrimal gland and duct atresia and atretic ear canals. Genetic testing confirmed the diagnosis of AEC syndrome with a heterozygous L514S mutation in the sterile alpha motif (SAM) domain of p63 (Payne et al., 2005). Her skin erosions were treated with topical bacitracin ointment under petrolatum gauze and ultimately healed by 4 weeks of age.

At 3 months of age, she was taken to the operating room for cleft lip adhesion and silicone nasal conformer placement. Three months later, she returned for definitive repair of her cleft lip with a modified Millard-type rotation-advancement and removal of the nasal conformer (Ruotolo et al., 2006). At the age of 16 months, she underwent repair of her cleft palate by Furlow double-opposing Z-plasty. Surgical wounds healed uneventfully following each procedure. Examination of her lip 27 months after cleft repair demonstrated a very satisfactory result (Fig. 2). She has not had any specific wound healing complications over the follow-up period, although she continues to have local scalp erosions with secondary infections.

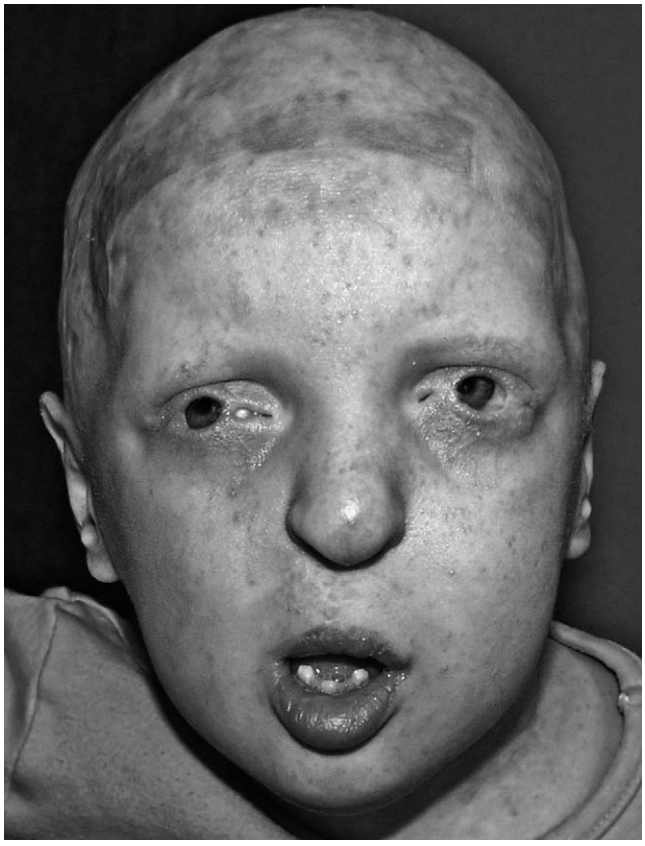

FIGURE 2 Satisfactory wound healing in patient A, shown here 27 months after cleft lip repair. Pinched ala nasi and a small mouth, characteristic features of the AEC syndrome facies, are also apparent. Bilateral medial and lateral tarsorrhaphies have been performed for corneal protection.

Case B

A full-term male infant presented with a moderately wide cleft of the secondary palate extending to the incisive foramen, erosive scalp dermatitis, hyponychia, hypoplastic nipples, webbed penis, and right ankyloblepharon. The oral mucosa was grossly normal. Genetic testing confirmed the diagnosis of AEC syndrome with a heterozygous R555P mutation in the SAM domain of p63 (Payne et al., 2005). Both parents were unaffected and denied a history of consanguinity. The patient's scalp erosions were treated by topical therapy with petrolatum gauze, silicon-based dressings, and topical antibiotics where needed. At 11 months of age, the patient underwent cleft palate repair by Furlow double-opposing Z-plasty. The patient's postoperative course was uneventful. He has not experienced any wound healing complications over the 18 months of postoperative follow-up.

Surgical procedures in both patients are standard approaches to the treatment of cleft palate and/or cleft lip utilized by the senior author. Whereas each procedure was individualized to

the patients' unique findings, no special repair was performed in consideration of the AEC syndrome diagnoses.

Discussion

The ectodermal dysplasias are a large group of clinically and genetically heterogenous disorders characterized by the abnormal development of one or more appendages of epidermal (hair, nails, teeth, sweat glands) or oral ectodermal origin. Ectodermal dysplasias may occur in isolation or as part of a syndrome associated with other clinical abnormalities. To date, more than 170 ectodermal dysplasia syndromes have been reported (Priolo and Lagana, 2001; Lamartine, 2003). The clinical presentations of many of these disorders overlap considerably, yet most retain their eponymous descriptions for historical reasons.

The presentation of ectodermal dysplasia with cleft palate and/or cleft lip encompasses three main diagnoses: EEC syndrome, AEC syndrome, and RHS. Although each syndrome is highlighted by a unique finding (ectrodactyly in EEC syndrome; ankyloblepharon in AEC syndrome; the lack of ectodactyly or ankyloblepharon in RHS), clinical redundancy among these disorders has led several authors to speculate that they may, in fact, be variable expressions of the same underlying abnormality (Cambiaghi et al., 1994; Rowan, 1996; Kannu et al., 2006). In support of this, Moerman and Fryns (1996) described a child with EEC syndrome who was born to a mother with RHS. Dianzani et al. (2003) and Steele et al. (2005) reported cases of the coexistence of RHS and AEC syndrome within the same family. Furthermore, several reports have presented data to show that RHS shares significant clinical overlap as well as very similar or identical mutations with both EEC and AEC syndromes (van Bokhoven et al., 2001; Bougeard et al., 2003; Dianzani et al., 2003; Kantaputra et al., 2003; Bertola et al., 2004; Chan et al., 2005; Shotelersuk et al., 2005; Kannu et al., 2006).

Most evidence, however, supports a genotype-phenotype correlation among the ectodermal dysplasia with clefting disorders (van Bokhoven and Brunner, 2002). With few exceptions, mutations in the DNA binding domain of p63 are responsible for EEC syndrome, whereas AEC syndrome is the result of missense mutations in the SAM domain of p63. Additional mutations in p63 also have been reported to cause other ectodermal dysplasia syndromes, including the split-hand/split-foot malformation (OMIM 183600), limb-mammary syndrome (OMIM 603543), and acro-dermato-ungual-lacrimal-tooth (ADULT) syndrome (OMIM 103285).

Although the molecular mechanistic links between these p63 mutations and the clinical presentations that result remain largely unknown, the critical role of p63 in epidermal and craniofacial development is evident in the dramatic phenotype of p63 knockout mice (Mills et al., 1999; Yang et al., 1999). These animals have truncated or absent limbs and lack stratified and pseudostratified epithelia and epithelial appendages such as mammary glands, hair follicles, and teeth. They fail to develop a mature epidermis and are covered only by a thin, single-cell layer that does not express epidermal differentiation markers. This leads to rapid water loss and death by dehydration within the first few hours of life. Similarly, the epithelium of the tongue and oral cavity in these mice is composed of a single cell layer that fails to express normal oral epithelial differentiation markers. A truncated secondary palate and hypoplastic maxilla and mandibula are present also.

In normal skin, p63 expression is limited to the basal and immediately suprabasal levels, corresponding to cells that are proliferating actively or have that potential (Parsa et al., 1999; Hall et al., 2000). In contrast, epidermal p63 expression in most patients with AEC syndrome extends beyond the basal proliferating cells into more suprabasal cells that normally undergo differentiation (McGrath et al., 2001). Along with this aberrant expression, several recent studies also have documented that AEC-associated mutations in p63 lead to altered cell proliferation, differentiation, and survival *in vitro* (Fomenkov et al., 2003; Beretta et al., 2005; Huang et al., 2005; Lo Iacono et al., 2006; Testoni and Mantovani, 2006). Exactly how these altered cellular functions lead to the AEC phenotype, however, remains unclear.

In addition to its role in the preservation of epidermal integrity through the maintenance of the proliferative potential of keratinocytes (Koster et al., 2004), p63 also may play an important role in wound healing (Noszczyk and Majewski, 2001; Bamberger et al., 2005). Nevertheless, the effect that mutations in p63 have on wound healing physiology remains uncertain. Several AEC syndrome patients presented at the Skin Erosion and Wound Healing in AEC Conference in 2003 had problematic, chronic wounds that failed treatment with extensive debridement and skin grafting. These wounds eventually healed with significant atrophic scarring (Siegfried et al., 2005). It is difficult, however, to isolate the particular effect of AEC syndrome on these poor wound healing outcomes, because all of these complications occurred in the setting of severe wound infections. Neither of our patients experienced an adverse wound healing event. Including the patients described here, 47 cases of AEC syndrome have been reported in the English literature. Of these, 18 provide information regarding the patients' cleft palate and/or cleft lip repair outcomes (Hay and Wells, 1976; Spiegel and Colton, 1985; Shwayder et al., 1986; Greene et al., 1987; Fosko et al., 1992; Vanderhooft et al., 1993; Satoh et al., 1994; Mancini and Paller, 1997; Zenteno et al., 1999; Tsutsui et al., 2003; Steele et al., 2005). No reports describe any wound healing complications, although one patient reported by Spiegel and Colton underwent ''multiple surgical procedures for repair and revision of the cleft lip and palate'' over approximately 20 years (Spiegel and Colton, 1985, p. 812). Two other cases, both in the original series by Hay and Wells, presented with oronasal fistulae following cleft palate surgery. This 17% (3/18) rate of secondary surgery is consistent with the incidence within the general cleft lip and palate population.

Summary

We herein describe two cases of Hay-Wells syndrome. Cleft lip and cleft palate repairs were performed in one patient. Cleft

palate repair alone was performed in the other. Postoperative wound healing proceeded uneventfully in both patients. This report, along with a review of 16 previously published cases, suggests that cleft repair in AEC patients can be performed without concern for increased wound healing complications. Future studies with a larger number of patients may be needed, however, to document more fully the association between secondary surgical complications and AEC syndrome.

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