

Gene p63: In ectrodactyly-ectodermal dysplasia clefting, ankyloblepharon-ectodermal dysplasia, Rapp-Hodgkin syndrome

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ABSTRACT

Introduction: An analysis was made of three different syndromes associated with p63 gene mutations, known as ectrodactyly-ectodermal dysplasia-clefting syndrome (EEC), ankyloblepharon-ectodermal dysplasia clefting syndrome (AEC or Hay-Wells) and Rapp-Hodgkin syndrome (RHS). The postoperative complications associated with their cleft reconstructions were also evaluated. **Materials and Methods:** Extensive demographic information, in particular of the clinical appearances, associated malformations, and the types and complications of the reconstructive surgical procedures, were recorded of these syndromic cases occurring in a database of 3621 facial cleft deformity patients. The data was analyzed using the Microsoft Excel program. **Results:** A total of 10 (0.28%) cases of p63 associated syndromes were recorded: EEC (6), RHS (3), and AEC (1). The following clinical cleft appearances were noted – EEC = 6: CLA 1 -right side unilateral (female); CLAP 4 – right side (1) + left side (1) unilateral (male + female); bilateral (2) (males); hPsP 1 (female) (divided in 3 Black, 2 White, 1 Indian); RHS = 3: CLAP 2 (White males); hPsP 1 (White female); AEC = 1: CLAP bilateral (White male). Other features of the syndromes were: skin, hand, foot, tooth, hair and nail involvement, and light sensitivity. Postoperative complications included: (i) stenosis of nasal opening, especially after reconstruction of the bilateral cleft lip and the columella lengthening (2 cases), (ii) premaxilla-prolabium fusion (2 cases), (iii) repeated occurrence of oro-nasal fistula in the hard palate (4 cases), and (iv) dysgnathial development of midfacial structures (3 cases). **Discussion:** Three different p63 associated syndromes (EEC, AEC, and RHS) were diagnosed (0.27% of the total facial cleft deformities database). The majority of the cases presented with a bilateral CLAP in males only. A number of females and males had unilateral CLA. The hPsP-cleft was recorded in females only. The associated ectodermal component most probably had a profoundly negative influence on postoperatively wound healing, which was observed in particular at the nasal openings, the premaxilla sulcus and in the hard palate mucosa. The reconstruction of p63 associated syndromes is a greater challenge than the usual cleft reconstruction to the surgeon.

Keywords: Ankyloblepharon-ectodermal dysplasia clefting syndrome, cleft lip, cleft palate, ectrodactyly-ectodermal dysplasia-clefting syndrome, p63 gene, Rapp-Hodgkin syndrome

INTRODUCTION

To evaluate three different syndromes clinically linked to p63 gene mutation, known as ectrodactyly-ectodermal dysplasia-clefting (EEC) syndrome, ankyloblepharon-ectodermal dysplasia clefting (AEC or Hay-Wells) syndrome and Rapp-Hodgkin (RH) syndrome, and reporting on their associated perioperative complications.

MATERIALS AND METHODS

A retrospective review of patients treated at the Cleft Palate and Facial Deformity Clinic of the University of Pretoria over the period August 1983-July 2010. The patient's charts were reviewed and the information was grouped into: Race, gender, family history, clinical features, and perioperative complications. The

clinical features were then subdivided into a triad of three major key features, Limb abnormalities, cleft deformities, and ectodermal dysplasia. Ectodermal dysplasia regarded malformations of the skin, nails, hair, ears, teeth, eyes, and urogenital tract [Table 1].

Ethical consideration

All participation was voluntary and written consent was given by patients or their parents. Approval was obtained from the Research Ethics Committee, Faculty Health Sciences, University of Pretoria, which complies with ICH-GCP guidelines and has US Federalwide Assurance.

Statistics

Their clinical appearances along with the cleft repair outcome were analyzed using descriptive statistics.

RESULTS

Out of a total of 3352 patients encountered at the Cleft Palate and Facial Deformity Clinic at the University of Pretoria, 10 cases were clinically linked to p63 syndromes of which 6 were linked to EEC syndrome (60%), 3 patients to RH syndrome (30%), and 1 patient to AEC syndrome (10%). All cases appear to be *de novo* events except one RH syndrome patient's mother had a history of achondroplasia. Out of the total of 10 patients linked to p63 syndromes, there were 1 Indian, 3 Black Africans, and 6 Caucasians. From the total patients linked to p63 syndromes the following gender ratio was found: RH syndrome had two males and one female. AEC syndrome manifested in one male and the EEC equally presented with three males and three females. The majority of the 10 cases presented with a bilateral cleft lip-palate (BCLP) [Figure 1], and this appeared only in males, and only females with a cleft palate (CP) deformity.

Eight of the ten patients underwent cleft surgery. Three of the eight patients, one with RH syndrome and two with EEC syndrome had additional surgery for velopharyngeal incompetence. Five out of eight patients presented with oro-nasal fistula, which was the most common complication encountered. Two patients, one AEC and one RH syndrome presented with similar complications

of nasal passage stenosis (webbing), and premaxillary mucosal fusion. Maxillary deficiency was noted in three patients; one RH and AEC syndrome patient, the third EEC syndrome patient required a Le Fort I osteotomy with rigid external distractor (RED).

One RH syndrome and one AEC syndrome patient suffered from recurrent otitis media and required myringotomies. A RH syndrome patient had excessive fibrosis at the soft and hard palate junction, postoperatively. Cheilitis angularis and chronic peri-oral ulcers with signs of hyperkeratosis were recurrent problems in the RH syndrome patients [Table 1].

The ectodermal dysplasia phenotype manifested in a wide variety of tissues. Hair and skin were mostly fine and sparse, with red pigmented hair noted in two cases. Nails were malformed in most patients [Figure 2] and also easily detachable in the AEC patient. Dental disorder included hypodontia and enamel malformation [Table 1]. Photophobia and ophthalmic infections were the most troublesome eye conditions for the majority of the study group [Figures 3 and 4].

Limb abnormalities were the major feature in the EEC syndrome group. All six patients had ectrodactyly of the feet. Four patients had ectrodactyly of the hands and two patients had syndactyly of the fingers and toes [Table 1]. No limb abnormalities were encountered in the RH syndrome group, but syndactyly of the 2-3 toes and nevi on the feet were present in the AEC syndrome patient. Other abnormalities included urogenital malformations, which was only found in RH and EEC syndrome patients [Table 1].

DISCUSSION

Different syndromes can result from different mutations in a single gene. Mutation in the p63 gene can cause at least five different syndromes: EEC (OMIM 604292),^[1] AEC and cleft lip/palate (OMIM 106260),^[2] Acro-Dermato-Ungual-Lacrimal-Tooth (ADULT) (OMIM 103285),^[3] RH (OMIM 129400),^[4] and Limb-Mammary Syndrome (LMS) (OMIM 603543).^[5] Two nonsyndromic human disorders are also caused by p63 mutation: Split-hand/split-foot malformation (SHFM 4), (OMIM 605289),^[6]

Table 1: Summary of patients linked to p63 syndromes

Syndrome	Cleft	Limb	Eyes	Skin	Nails	Hair	Ears	Teeth	Other
RH	CP	-	Photophobia	-	Dystrophic	Sparse hair	-	-	Hyperplastic mucosa
RH	CLP	-	Photophobia	Dry	Dystrophic	Dry, red	-	Enamel malformed	Cheilitis angularis, renal dysplasia, inguinal hernia, Urethral reflux
RH	CLP	-	-	-	Dystrophic	Sparse	-	-	Thin mucosa, Peri-oral ulcers
AEC	CLP	Syndactyly	Ankyloblepharon Photophobia, infections	Dry, nevi	Loose	Brittle white, sparse eyebrows and eyelashes	Otitis media	-	-
EEC	CLP	Ectrodactyly	-	-	-	-	-	Hypodontia, Enamel malformation	-
EEC	CLP	Ectrodactyly	Blue sclera	-	-	-	Cupped	-	Micropenis, cryptorchidism
EEC	CP	Ectrodactyly	-	Dry	-	Red	-	Hypodontia, Enamel hypoplasia	-
EEC	CLP	Ectrodactyly	Conjunctivitis, Lacrimal duct atresia	-	-	Brittle, white	-	Hypodontia	Urethral pathology
EEC	CLP	Ectrodactyly, Syndactyly	Infections	-	-	-	-	-	Umbilical granuloma
EEC	CL	Ectrodactyly, Syndactyly	-	Thin	Dystrophic	Sparse	-	Hypodontia	Hyperplastic mucosa

RH = Rapp-Hodgkin, CLP = Cleft lip-palate, AEC = Ankyloblepharon-ectodermal dysplasia clefting, EEC = Ectrodactyly-ectodermal-dysplasia-clefting

and nonsyndromic cleft lip/palate (NSCL/P) (OMIM 119530).^[7]

p63 is a member of the transcription factor family and does not represent a classic tumor suppressor gene as p53. p63 is rather a key regulator in limb, epithelial, and craniofacial development. In the histochemical analyses of laboratory mouse embryos, high p63 levels were found in epithelial cells, especially in stem cell population of epithelial tissue such as basal cells of the tongue, cervix, mammary gland, esophagus, prostate, and urothelium.^[8,9]

AEC syndrome is clinically distinct due to the presence of ankyloblepharon, absence of limb abnormalities such as ectrodactyly and the presence of severe scalp lesions.^[2,10] The one patient clinically linked to AEC syndrome in this study had a history of ankyloblepharon that was surgically corrected shortly after birth. The ectodermal dysplasia phenotype in this study group was less severe than that reported in most studies.^[10,11] Peeling of the palms was the only erosive skin lesion reported. Limb abnormalities can include syndactyly but seldom ectrodactyly. Syndactyly as in this patient was more commonly reported in RH than AEC syndrome.^[11]

RH syndrome is similar to AEC syndrome when comparing their facial cleft and limb malformations. These two syndromes are considered by many authors to be variable expressions of the same disease.^[12,13] RH syndrome patients are characterized by certain facial features that were consistent with the patients studied at the University of Pretoria [Table 1]. These peculiar features include: High hairline, narrow pinched nose, low nasal

bridge, sparse facial hair, and hypoplastic midface structures.^[12,14] The dystrophic nail and hair phenotypes were the most commonly encountered in the study group, with less features of dental deformities, ear abnormalities, and skin erosions [Table 1].

EEC syndrome patients resemble the prototype of the p63 syndrome family, featuring the complete triad of facial clefting, ectodermal dysplasia, and limb abnormalities.^[15,16] Limb abnormalities are a key feature in the clinical diagnosis of patients with EEC syndrome and are observed in 84-90% of cases.^[11,16] All the patients in the

Table 2: Comparative analysis of surgical complications

Authors	AEC (%)	RHS (%)	EEC (%)
Growth deficiency			
van Bokhoven and Brunner, 2002 ^[21]	+	-	+
van Straten and Bütow, current study	100	33	17
Birgfeld <i>et al.</i> , 2007 ^[22]	61	-	-
Hart and Kyrkanides, 1994 ^[14]	-	100	-
Farrington and Lausten, 2009 ^[23]	-	-	100
Wojcicki <i>et al.</i> , 2010 ^[24]	-	-	30
Oro-nasal fistula			
van Straten and Bütow, current study	100	33	50
Cabiling <i>et al.</i> , 2007 ^[28]	16.6	-	-
Wojcicki <i>et al.</i> , 2010 ^[24]	-	-	60
Mucosal fusion			
van Straten and Bütow, current study	100	67	34
Wojcicki <i>et al.</i> , 2010 ^[24]	-	-	60

+ Indicated/- Not indicated, AEC = Ankyloblepharon-ectodermal-dysplasia clefting, RHS=Rapp-Hodgkin syndrome, EEC=Ectrodactyly-ectodermal-dysplasia-clefting



Figure 1: AEC syndrome (Bilateral CLP)



Figure 2: Ectodermal Dysplasia Nail abnormalities



Figure 3: Low set ears. Retrognathic maxilla



Figure 4: Course hair. Spares eyebrows and eyelashes. Photophobia

EEC syndrome study group had ectrodactyly of the feet and four had additional hand ectrodactyly features [Table 1].

The p63 gene is known to be important not only in limb, craniofacial, and ectodermal development, but also in epithelial integrity and wound healing.^[8,17] Eight patients had surgical interventions [Table 1]. Five out of eight patients presented with oro-nasal fistula, which was the most frequent complication encountered. Out of the five patients were three with EEC syndrome, one with AEC syndrome and one RH syndrome. Patient No. 8 [Table 1] required multiple surgeries, for example, a local temporal muscle flap to repair his oro-nasal fistula. These figures compare with the study by Wojcicka *et al.*, who reported on an increased incidence of complications [Table 2].

Two patients, one AEC and one RH syndrome presented with similar complications of nasal passage stenosis (webbing), and premaxillary mucosal fusion leading to breathing problems and difficulties with nasal intubation. None of these complications were prevalent in other studies devoted to cleft repair of p63 patients.

One RH syndrome and one AEC syndrome patient both suffered from recurrent otitis media and required meringotomies. This complication is mostly due to poor middle ear ventilation a result of the abnormal tensor veli palatini muscle insertion in cleft patients. This complication is considerably less than what is encountered in the literature.^[18-20] Bütow *et al.*^[20] gave a detailed account of the importance of activating the tensor veli palatini muscle and its function on the eustachian tube. This procedure is standard protocol in soft palate repair at the Cleft and Facial Deformity Clinic of the University of Pretoria, and a possible reason for this low complication rate.

Maxillary deficiency was noted in three patients; one EEC syndrome patient who had a Le Fort I osteotomy with RED; one patient with RH syndrome; and one with AEC syndrome. These results compared well with international literature, reporting an increased incidence compared with general cleft patients [Table 2]. It must be noted that all the patients considered in this study are not at an age where comments can be made concerning their facial growth potential^[14,21-24] [Table 2]. It seems that the poor oral environment, diminished salivary gland function and poor healing abilities lead to more cleft repair considerations than for the general cleft population.^[12,23,25-27]

CONCLUSIONS

We describe 10 patients clinically linked to p63 mutation and report complications associated with cleft repair. This report suggests that there is an increased incidence of complications due to the ectodermal dysplasia component, that has a direct negative influence on wound healing and must be considered in cleft surgery.

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