

CASE REPORT

Two case reports with literature review of the EEC syndrome: Clinical presentation and management

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Abstract

We report on siblings who suffer from EEC syndrome and show our experiences of the "Basel concept" of cleft lip/palate repair based on the early, one-stage closure of all components. It is performed in the age of 3–4 months to provide early normal conditions for anatomy and muscle function.

Key words:

EEC syndrome, lip adhesion, "all-in-one"-concept

History

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Introduction

The syndrome with ectrodactyly, ectodermal dysplasia, cleft lip and cleft palate (EEC) is a complex disease with a variety of abnormalities of the ectodermal and mesodermal germinal layer. The first author who described this disease was Eckoldt [1,2] in 1804. Split hands or feet are characterized by agenesis of the third ray and possible fusion of the remaining fingers or toes. The ectodermal component of this syndrome includes hair with hypotrichosis, hypopigmentation, the teeth with hypodontia, enamel hypoplasia and microdontia and ultimately the nails, which present themselves dystrophic in most cases. Variable appears hypohidrosis [3]. A number of associated anomalies are also frequently found. In the 230 published cases, 84% of patients presented with split hands or feet. Dysplasia of the ectoderm arises in 77% of patients and clefts appear in 68% of cases. Important hints may indicate an EEC syndrome already in the clinical examination of the patient and in the investigation of family history.

Two case reports of our department shall demonstrate the management of EEC syndrome affected patients with "all-in-one" closure of the lip cleft and palate cleft and the treatment regimen in manifest ectodermal dysplasia.

Case 1

A newborn baby with a unilateral complete cleft lip and palate (left side- cleft palate width 23 mm) – first child of

non-consanguineous marriage – was referred to our department. Additionally, the child presented a deletion of the central finger on the right hand and fusion of the second and third finger on the left hand as well as fusion of the second and third toe on both feet. Paper-thin, dry and reddened skin and sparse scalp hair were also visible (Figure 1). Further biochemical and echocardiographic examinations showed no pathological findings. The father suffered from the EEC syndrome, too-, showing similar hand malformation and a bilateral cleft lip and palate, which was treated in multiple surgeries. In our patient, the genetic analysis showed the karyotype arr11q25 (129'994'805-134'938'470) × 1. Feeding of the child was possible with a palate obturator. For (nasal) alveolar molding lip taping with an elastic plaster (DynaCleft®, Barrie ON, Canada) was done. At the age of 4 months, the cleft lip width was still 12 mm. For improved soft-tissue conditioning, lip adhesion was planned (Figure 2). Two months later, the one-step procedure of the cleft lip and palate closure was performed. The operative procedure involves firstly in intravelar veloplasty with microscopic view, secondly in restore the nasal floor with two choanes and pedicled flaps without push back and at the end doing only a gingivoperiosteoplasty but without touching the germ area. At the end, a palatal plate was fitted for 7 days. In our protocol, we do a secondary osteoplasty with 9/10 years of age. The operation time was 60 min for the palate. During the closure of the palate to prevent pressure damage on the

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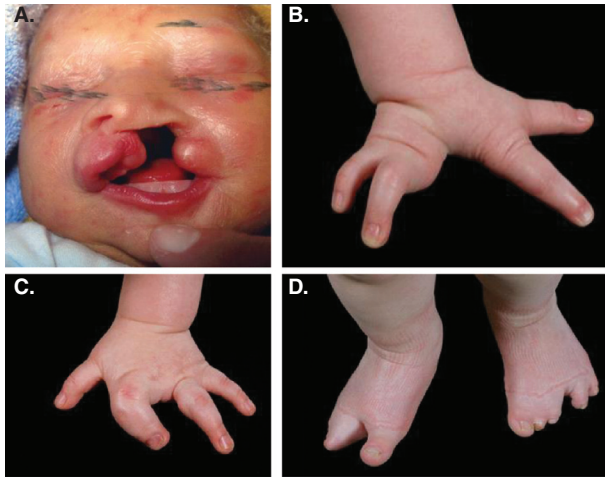


Figure 1. The clinical examinations showed a complete cleft lip and palate (left side) and deletion of the central finger on the right hand, fusion of second and third finger of the left hand and fusion of the second and third toe on both feet.

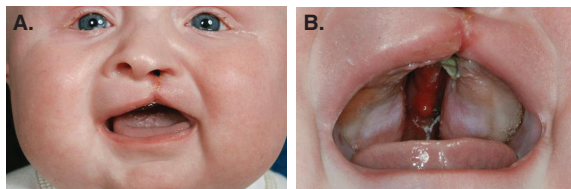


Figure 2. After lip adhesion, 4 months of age.

tongue the mouth gag was often released. Nevertheless, after surgery, the child had to be re-intubated at the intensive care unit due to an exfoliative stomatitis and dramatic swelling of the back of the tongue with impairment of the upper respiratory tract (Figure 3). Our patient did not suffer from neither micrognathia nor macroglossia. It was only the postoperative tongue swelling that caused the respiratory problems. Supportive treatment with an anti-edematous and anti-inflammatory medication (cortisone intravenously) was initiated. The patient could be ex-tubated 16 h later. The further post-operative course of treatment was without complications (Figure 4). We suppose that there is a connection with the EEC which makes the tissue more sensitive – but this is a hypothesis that is not proven.

Until now, no treatment concerning hands and feet was performed.



Figure 3. Swelling of the back of the tongue and exfoliation after the “all in one” closure and before re-intubation.



Figure 4. Follow-up 6 months after surgery with harmonious upper lip and no abnormalities in the epidermis.

Case 2

This case presents the sister of the above described boy, born 3 years and eight months later: Born at 38 week of gestation with a birth weight of 2'985 g she showed a bilateral cleft lip, syndactyly on all extremities and a conspicuous dryness of the skin (Figure 5). Clinical findings and the family history lead again to the EEC syndrome. Similar to the brother an obturator plate with nasoalveolar molding was adapted. At the age of 8 weeks a lip adhesion was performed. With 4.5 months, the one-stage closure of bilateral cleft lip and palate was performed. The postoperative course of treatment was uneventful (Figure 6).

Until now, no treatment concerning hands and feet was performed.



Figure 5. The clinical examination of the patient 3 h after birth shows the typical characteristics for the EEC-syndrome.



Figure 6. Follow-up 4.5 months after surgery. No complications have occurred in wound healing due to the EEC-syndrome

Discussion

The abbreviation EEC was first proposed by Rüdiger et al. [3] characterized by ectrodactyly, ectodermal dysplasia, cleft lip and/or cleft palate. Since then, numerous reports in the literature have expanded the clinical appearance. The transmission is usually autosomal-dominant trait with variable expressivity and reduced penetrance [4-6]. The prevalence is estimated to be 1 case per 1.5 million live births [6]. Some authors believe that the classic case of the EEC syndrome is caused by mutation of the p63 gene [7]. The variability in the phenotypic expression is explained by the interaction of ectodermal with the mesodermal germ layer [8].

The EEC syndrome must be differentiated from other syndromes, which also show an ectodermal dysplasia and orofacial clefts as the Rapp-Hodgkin syndrome [9], the AEC syndrome (syndrome with ankyloblepharon filiform adnatum, ectodermal dysplasia and cheilognathopalatoschisis, [10-12]). Usually, all these syndromes show normal limbs. Others have their own characteristics, for example the Rapp-Hodgkin syndrome presenting a short stature and special lineaments. All these diseases and the EEC syndrome have a large variability in gene expression. They can be oligosymptomatic, and their expression may vary. The EEC syndrome has to be distinguished from other diseases with acral anomalies and oral cleft, including the acrorenal 'syndrome' [13] and from the fetal alcohol syndrome [14]. Minor anomalies of the EEC syndrome are renal malformations, deafness, mental retardation [15] and choanal atresia [16]. Other recently reported associated anomalies are the insufficiency of the pituitary gland [17], anorectal malformations [18,19] and hypoplasia of the thymus [20].

Until now, three types of EEC syndrome and their respective gene loci were molecularly identified. Balanced chromosome changes or interstitial deletions were found: type 1 is linked to gene locus 7q11.21-q21.3, type 2 and type 3 with chromosome 19 locus with 3q21 (p63) [21-23]. Recently, heterozygous mutations in the p63 gene have been shown to 3q27 by amino acid substitutions in the DNA-binding domain, which are considered as the main cause for the formation of the gap in hands and feet [25-27].

The ultrasound in prenatal diagnosis plays an important role in the early detection of ectrodactyly and cleft lip and palate [28-30]. For a more accurate prenatal diagnosis of this syndrome, a molecular study was introduced. With the use of a DNA extraction from fetal chorionic villi [31], a prenatal DNA analysis can be carried out in a pregnancy at risk for

the EEC syndrome. Addition accurate clinical assessment after birth is mandatory.

At our centre, EEC children will be treated like other non-syndromic cleft patients. In the first 24 h after birth, an obturator plate and if necessary and due to dry skin possible, upper lip taping is adapted for alveolar molding. The gastric tube see in Figure 4 was removed after the obturator plate was inserted. If the cleft lip remains more than 15 mm a lip adhesion is an option. Normally, this will be performed at the age of 8 weeks, in the first case it was delayed due to surrounding circumstances. Approximately 8 weeks later, a closure of all layers in a single operational step will be performed. One-stage procedures with 3-4 months can lead to disturbance in growth of the maxilla, but the extend was similar to the mean values of multistage procedures assessed in the Eurocleft study [32]. Thus, normal conditions for further development can be achieved. Children and their parents have no further psycho-social stress due to multiple surgical interventions at an early age. A normal family life and normal language development are possible. The main therapeutic approach depends on the expression of the ectodermal dysplasia and should be evaluated individually for each patient. It is mandatory that the patient has a close follow-up with, if necessary, functional physiotherapy, speech therapy and early functional orthodontic care. The optimal treatment of these patients can only be achieved in an interdisciplinary way.

Conclusion

Whenever cases of EEC syndrome occur, it is important, according to their phenotypic characteristics, to follow an interdisciplinary approach to reduce complications, to minimize undesirable sequelae and provide the best possible medical care.

Ethics and consent: A written consent from the parents for the publication of photos is available.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

- [1] Eckoldt JG, Martens FH. Über einer sehr komplizierten Hasenscharte. Leipzig: Steinacker Publisher; 1804.
- [2] Annaren G, Andersson I, Lindgren PG, Kjartansson S. Ectrodactyly-ectodermis dysplasia-cleftin syndrome (EEC): the clinical variation and prenatal diagnosis. *Clin Genet* 1191;40:257-62.
- [3] Rüdiger RA, Haase W, Passarge E. Association of ectrodactyly, ectodermal dysplasia and cleft-lip-palate the EEC Syndrome. *Am J Dis Child* 1970;120:160-3.
- [4] Roelfsema NM, Cobben JM. The EEC syndrome: a literature study. *Clin Dysmorphol* 1996;5:115-27.
- [5] McNab AA, Potts MJ, Welham RAN. The EEC syndrome and its ocular manifestations. *Br J Ophthalmol* 1989;73:261-4.
- [6] Kong T, Temple IK, Baraitser M. Dilemmas in counselling: the EEC syndrome. *J Med Genet* 1990;27:752-5.
- [7] Brunner HG, Hamel BCJ, van Bokhoven H. The p63 gene in EEC and other syndromes. *J Med Genet* 2002;39:377-81.

- [8] Barrow LL, van Bokhoven H, Daack-Hirsch S. Analysis of the p63 gene in classical EEC syndrome, related syndromes, and non-syndromic orofacial clefts. *J Med Genet* 2002;39:559–66.
- [9] Rapp HS, Hodgkin WE. Anhidrotic ectodermal dysplasia: autosomal dominant inheritance with palate and lip anomalies. *J Med Genet* 1968;5:269–72.
- [10] Rogers JW. Ankyloblepharon filiforme adnatum. *Arch Ophthalmol* 1961;65:114–17.
- [11] Long JC, Blandford SE. Ankyloblepharon filiforme adnatum with cleft lip and palate. *Am J Ophthalmol* 1962;53:126–9.
- [12] Hay RJ, Wells RS. The syndrome of ankyloblepharon, ectodermal defects and cleft lip and plate: an autosomal dominant condition. *Br J Dermatol* 1976;94:277–89.
- [13] Curran AS, Curran JP. Associated acral and renal malformations: A new syndrome? *Pediatrics* 1972;49:716–25.
- [14] Herrmann J, Pallister PD, Opitz JM. Tetraectrodactyly and other skeletal manifestations in the fetal alcohol syndrome. *Eur J Pediatr* 1980;133:221–6.
- [15] Rodini ESO, Richieri-Costa A. EEC syndrome: report on 20 new patients, clinical and genetic considerations. *Am J Med Genet* 1990;37:42–53.
- [16] Christodoulou J, McDougall PN, Sheffield LJ. Choanal atresia as a feature of ectrodactyly-ectodermal dysplasia-clefting (EEC) syndrome. *J Med Gene* 1989;26:586–9.
- [17] Gershoni-Baruch R, Goldscher D, Hochberg Z. Ectrodactyly-ectodermal dysplasia-clefting syndrome and hypothalamo-pituitary insufficiency. *Am J Med Genet* 1989;68:168–72.
- [18] De Smet L, Fryns JP. Anal atresia and abdominal wall defect as unusual symptoms in EEC syndrome. *Genet Couns* 1989;6:127–30.
- [19] Majewski F, Goecke T. Rectal atresia as rare manifestation in EEC syndrome. *Am J Med Genet* 1996;63:190–2.
- [20] Frick H, Munger DM, Fauchere JC, Stallmach T. Hypoplastic thymus and T-cell reduction in EECUT syndrome. *Am J Med Genet* 1997;69:65–8.
- [21] Celli J, Duijf P, Hamel BC, Bamshad M, et al. Heterozygous germline mutations in the p53 homolog p63 are the cause of EEC syndrome. *Cell* 1999;99:143–53.
- [22] Ray AK, Marazita ML, Pathak R, Beever CL, et al. TP63 mutation and clefting modifier genes in an EEC family. *Clin Genet* 2009;66:217–22.
- [23] Gurnett CA, Dobbs MB, Nordsieck EJ, Keppel C, et al. Evidence for an additional locus for split hand/foot malformation in chromosome region 8q21.11-q22.3. *Am J Med Genet A* 2006;140:1744–8.
- [24] Hennekam RCM, Krantz ID, Allanson JE. *Syndromes of the head and neck*. 5th edition. New York: Oxford University Press; 2010. p 974–8.
- [25] Celli J, Duijf P, Hamel BC. Heterozygous germline mutations in the p53 homolog p63 are the cause of EEC syndrome. *Cell* 1999;99:143–53.
- [26] Ianakiev P, Kilpatrick MW, Toudjarska I, Basel D, et al. Split-hand/split-foot malformation is caused by mutations in the p63 gene on 3q27. *Am J Hum Genet* 2000;67:59–66.
- [27] McGrath JA, Duijf PH, Doetsch V. Hay-Wells syndrome is caused by heterozygous missense mutations in the SAM domain of p63. *Hum Mol Genet* 2001;10:221–9.
- [28] Anneren G, Andersson T, Lindgren PG, Kjartansson S. Ectrodactyly-ectodermal dysplasia-clefting syndrome (EEC): the clinical variation and prenatal diagnosis. *Clin Genet* 1991;40:257–62.
- [29] Bronshtein M, Gershoni-Baruch R. Prenatal transvaginal diagnosis of the ectrodactyly, ectodermal dysplasia cleft palate (EEC) syndrome. *Prenat Diagn* 1993;13:519–22.
- [30] Leung KY, MacLachlan NA, Sepulveda W. Prenatal diagnosis of ectrodactyly: the lobster claw anomaly. *Ultrasound Obstet Gynecol* 1995;6:443–6.
- [31] South AP, Ashton GH, Willoughby C. EEC (ectrodactyly, ectodermal dysplasia, clefting) syndrome: heterozygous mutation in the p63 gene (R279H) and DNA-based prenatal diagnosis. *Br J Dermatol* 2002;146:216–20.
- [32] Mueller AA, Zschokke I, Brand S, Hockenjos C, et al. One-stage cleft repair outcome at age 6- to 18-years -a comparison to the Eurocleft study data. *Br J Oral Maxillofac Surg* 2012;50:762–8.