PORTUGUESE JOURNAL OF PEDIATRICS

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CASE REPORT

Rare ectodermal dysplasia present at birth: regarding a case report

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Abstract

Introduction: Ankyloblepharon-ectodermal defects-cleft lip/palate (AEC) syndrome/Hay-Wells syndrome, is a rare disease, with autosomal dominant transmission, caused by mutations in the TP63 gene, which encodes a developmental transcription factor in the embryonic ectoderm. 70% of cases occur sporadically with no previous family history. It presents at birth and diagnosis is based upon the identification of distinctive signs of a child's phenotype. Molecular genetic tests confirm the diagnosis if TP63 gene mutation is detected. **Case report:** The authors describe the case of a newborn that presented at birth with areas of de-epidermization of the scalp, back, and scrotum, erythroderma, nail dystrophy, and posterior cleft palate. Genetic screening showed a heterozygous mutation of the TP63 gene. He is currently two years old, showing good clinical development, and in terms of his psychomotor development, he has a speech/language delay. **Discussion:** The approach is multidisciplinary and therapy is symptom-guided, correcting the cleft palate/lip, promoting skin barrier integrity, and accelerating the epidermization process. Genetic counseling/psychological support are recommended.

Keywords: Newborn. AEC syndrome. Ectodermal dysplasia. Genetic. Case report.

Displasia ectodérmica rara presente ao nascimento: a propósito de um caso clínico

Resumo

Introdução: A síndrome AEC (*ankyloblepharon, ectodermal defects, cleft lip/palate*)/*Hay-Wells syndrome*, doença rara, de transmissão autossómica dominante, é causada por mutações no gene TP63, que codifica um fator de transcrição do desenvolvimento ectodérmico embrionário. 70% dos casos ocorrem esporadicamente, sem história familiar prévia. Presente ao nascimento, o diagnóstico é baseado nos sinais característicos do fenótipo da criança. Testes genéticos moleculares confirmam o diagnóstico ao detetar a mutação no gene TP63. **Relato de caso:** Os autores descrevem o caso de um recém-nascido, ao nascimento com áreas de desepidermização no couro cabeludo, dorso e bolsa escrotal, eritrodermia, distrofia ungueal e fenda palatina posterior. O rastreio genético revelou uma mutação heterozigótica - gene TP63. Atualmente com dois anos, boa evolução clínica e atraso fonoaudiológico relativamente ao desenvolvimento psicomotor. **Discussão:** A abordagem é multidisciplinar, a terapia guiada pela sintomatologia, corrigindo a fenda/lábio palatino, promovendo a integridade da barreira cutânea e acelerando o processo de epidermização. Aconselhamento genético/apoio psicológico são recomendados.

Palavras-chave: Recém-nascido. Síndrome AEC. Displasia ectodérmica. Genética. Caso clínico.

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Received: 09-04-2023
Accepted: 12-09-2023
https://pjp.spp.pt

Available online: 10-04-2024
Port J Pediatr. 2025;56(1):52-56
DOI: 10.24875/PJP.M24000443

Keypoints

What is known

- Ankyloblepharon-ectodermal defects-cleft lip/palate (AEC) syndrome/Hay-Wells syndrome, is a rare disease, with autosomal dominant transmission caused by mutations in the sterile alpha motif (SAM) domain of the TP63 gene. These TP63 mutations lead to a varied range of phenotypes in patients affected by AEC syndrome. Seventy percent of cases occur sporadically, with no previous family history.
- The clinical findings of AEC syndrome can overlap with those of other ectodermal dysplasia syndromes and are heterogenous in presentation, complicating the diagnosis and additional characterization of these disorders.
- An individualized, multidisciplinary, and long-term follow-up should be guaranteed for affected subjects and their families, aimed at identifying associated morbidities and preventing and/or mitigating potential serious complications and adverse outcomes.

What is added

- The authors highlight the atypical presentation of this case since the diagnosis was made in the absence of ankyloblepharon, which is part of the classic triad of this syndrome's features.
- The field of genetics is constantly evolving and new methods of addressing these rare syndromes will continue to grow and begin to define a new era in genetic epidemiology.
- Multidisciplinary monitoring is key to providing early intervention in the light of findings, especially those unrelated to dermatological changes, that are present in this syndrome.

Introduction

Ankyloblepharon-ectodermal dysplasia-cleft lip/palate (AEC) syndrome, also known as Hay-Wells syndrome, belongs to a large, heterogeneous group of ectodermal dysplasias that affect the embryonic development of ectodermal tissues[1]. It is a rare genetic disorder, with about 100 patients reported to date. The female to male ratio is 1:1[2]. The exact prevalence is unknown due to the number of distinct ectodermal dysplasia syndromes and ambiguous definitions because of overlapping phenotypes and genotypes[1,2].

AEC syndrome is associated with a heterozygous mutation of the tumor protein p63 (TP63) gene, an important regulatory gene encoding a developmental transcription factor in the embryonic ectoderm that appears to control processes related to epidermal proliferation and differentiation. These TP63 mutations lead to a range of different phenotypes in patients affected by AEC syndrome[1,3].

Seventy percent of AEC syndrome cases occur sporadically with no previous family history (new or "*de novo*" mutation), with only thirty percent having an affected parent[4].

This syndrome is present at birth and diagnosis is based on the child's phenotypic features, a detailed clinical history, and a thorough clinical evaluation. A variety of specialized tests can aid in the diagnosis. Molecular genetic tests confirm AEC syndrome when they detect the mutation in the TP63 gene[4].

The authors seek to describe the case of a male newborn that presented at birth with a phenotype compatible with AEC syndrome, with a heterozygous mutation for the TP63 gene, as it is a rare disease with very few cases reported worldwide.

Case report

Term, caucasian newborn, 38 weeks post-menstrual age, who is the result of an uneventful pregnancy, monitored in primary health care, with healthy, non-consanguineous parents. It is of note that a 4th-degree maternal cousin has ectodermal dysplasia. Prenatal diagnosis of cleft palate in prenatal ultrasound at 21 weeks and an amniocentesis showed 46 XY. Negative serology and negative group B streptococcus screening test. For prolonged rupture of membranes (> 18 hours) the mother received three doses of intrapartum ampicillin prophylaxis.

A boy, weighing 2960 g and measuring 48.5 cm in length, with a head circumference of 34.5 cm, an Apgar score of 9/10 with good adaptation to extra-uterine life and no oxygen requirement, was born by vaginal delivery. At birth, he presented with extensive areas of de-epidermization and erosions of the scalp, back, and scrotum, erythroderma, nail dystrophy, and posterior cleft palate (Fig. 1A-D).

Due to the risk of infection, the newborn underwent blood tests and cultures for infectious screening, that came out negative, and was started on empiric antibiotics with ampicillin and gentamicin, completing eight days of antibiotic therapy.

Because of the large transdermal losses, the newborn required intravenous hydration during his first days and treatment with topical antibiotics/antifungals and emollient/re-epithelizing creams.

The congenital cardiopathy screening was negative. Ophthalmological evaluation was normal. The head, abdominal, and pelvic ultrasound, as well as the hearing screening, were normal. The heart ultrasound

Figure 1. A-D: phenotypic features at birth showing de-epidermization and erosions of the scalp, back, and scrotum, erythroderma, and nail dystrophy.

revealed an ostium secundum-type interatrial communication with mild left to right shunt.

The skin lesions presented with good clinical development, with gradual epidermization and resolution of the erosions. He was discharged at 13 days of age, clinically well, and with adequate ponderal development. He was to undergo multidisciplinary monitoring with dermatology, pediatric surgery, otolaryngology, and neonatology consultations.

Given the patient's phenotypic features, a diagnostic hypothesis of AEC/Hay-Wells syndrome was considered, and skin biopsy and genetic testing were performed.

The skin biopsy revealed mainly surface erosions and atrophy of the sebaceous glands, that although not specific, are described in AEC syndrome. The genetic testing identified a heterozygous mutation of the TP63 gene and based on the clinical and genetic findings, a diagnosis of AEC syndrome was made. The newborn was then referred for genetic consultation. Gene sequencing was extended to the parents, with the results pending.

A dermatology follow-up consultation at approximately one and a half months old showed good clinical development (Fig. 2A-D).

The cleft palate was surgically repaired at the age of 14 months, which was uneventful. The boy was then referred for a physical medicine and rehabilitation consultation. Due to a speech/language delay in terms of his psychomotor development, speech therapy was initiated.

He is currently 26 months old, presents with dysmorphic facial features, has a good weight-growth development according to his age and aside from a speech/language delay, has adequate psychomotor development with regular acquisition of neuromotor milestones. He also experiences chronic middle ear infections (otitis media) with no apparent development of hearing loss. The child remains under close dermatological follow-up in consultations and still requires topical emollient/re-epithelizing creams, showing hypotrichosis and sparse, brittle hair, a dry scalp with flaking on the surface, and nail dystrophy with micronychia. The skin is dry mainly due to some hypohidrosis.

Discussion

AEC syndrome is a form of ectodermal dysplasia, a group of conditions characterized by a wide variety of symptoms that can affect the skin, hair, nails, teeth, certain glands, and other ectodermal structures. The symptoms are highly variable with a broad clinical spectrum evident at birth[5].

Most newborns will have some degree of skin erosion, ranging from the mild involvement of a specific area to the severe, even life-threatening, involvement of the whole body. The scalp is most frequently involved and is usually affected more severely than other areas. Scalp erosions may lead to severe scarring and alopecia. Skin erosions can be recurrent throughout childhood, often involving the head and neck, palms, soles, and skin folds. Both hyperpigmentation and hypopigmentation are noted in nearly all individuals with AEC syndrome. Hair is light-colored and brittle, and eyelashes and eyebrows are usually sparse or absent. Nails are absent or dystrophic and dental abnormalities, including hypodontia and conical teeth, are common. Additional skin abnormalities may also be present. The characteristic skin erosions may be associated with a diffuse reddish coloration (erythroderma)[4,6]. Cleft palate with or without cleft lip occurs in all AEC syndrome patients. Some children experience chronic middle ear infections (otitis media) and approximately 90% develop hearing loss due to the failure of sound waves conducted through the middle ear, that can lead to conductive hearing loss and subsequent delays in speech development. Conversely, rare clinical findings, including heart defects, may occur[4,7]. Aside from

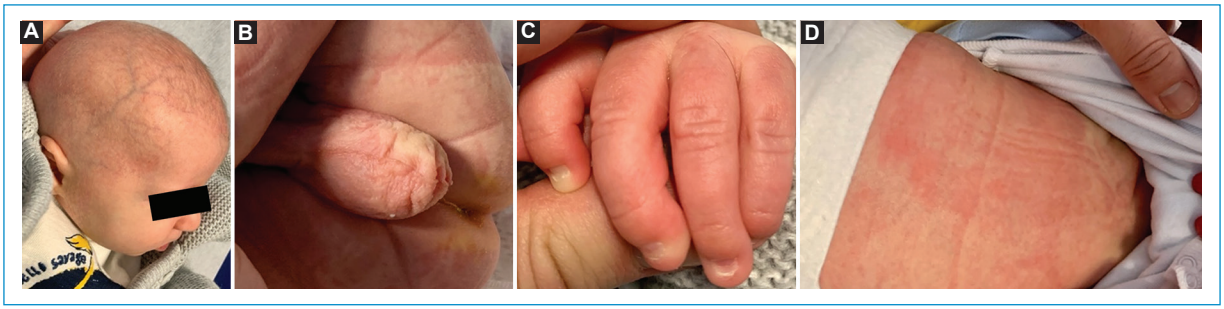

Figure 2. A-D: complete epidermization. Erythema on scalp and back. Less dystrophic nails.

the dental alterations, the features mentioned above were all observed in our newborn.

AEC syndrome may also cause decreased sweat production, resulting in thermal intolerance. Hypohidrosis is due, in part, to a lower number or absence of sweat glands[4]. Other glands may also be affected, such as in our case with the skin biopsy showing atrophy of the sebaceous glands.

Approximately 70% of individuals with AEC syndrome have ankyloblepharon filiforme adnatum (fusion of the eyelids), which can be partial, nearly complete, or even just a decrease in the size of the palpebral fissure[6,8].

Other rare clinical findings include ear canal atresia, supernumerary nipples, limb anomalies, and hypospadias. Poor weight gain, growth deficiencies, and short stature can also occur[4].

AEC syndrome has many clinical features in common with other TP63-related disorders that are forms of ectodermal dysplasia syndromes, such as ectrodactyly-ectodermal dysplasia-clefting (EEC) and Rapp-Hodgkin syndrome (RHS), the most important differential diagnosis for Hay-Wells Syndrome. Ankyloblepharon, when present, differentiates AEC syndrome from the other two conditions, although the degree of ankyloblepharon can vary and it may not be present in about 30% of patients, as in our case and others reported in literature. Clinical distinction between RHS and AEC syndrome is no longer considered important. Many reports indicate that AEC syndrome and RHS syndrome may be the same disease presenting differently. The minor differences between the two also suggest that these syndromes are variants of a single clinical entity. A recent review suggests that scalp erosions, rather than ankyloblepharon, may be the most important feature for distinguishing AEC and RHS from other p63-associated clefting and ectodermal dysplasia syndromes[6,8].

Due to the presence of erythrodermia and extensive areas of erosion, differential diagnoses should also include ichthyosis and epidermolysis bullosa, from which, however, AEC syndrome is distinguished by the occurrence of eye alterations or cleft lip/palate. It is thought that scalp lesions can disappear with age or lead to alopecia[9,10].

Curly hair-ankyloblepharon-nail dysplasia (CHAND) syndrome also has overlapping features with AEC syndrome but does not have skin erosions or cleft lip/palate[6].

A diagnosis of AEC syndrome is then based upon identifying characteristic symptoms, a detailed patient history, and a thorough clinical evaluation. A variety of specialized tests can aid in a diagnosis. Molecular examination of small samples of skin tissue (skin biopsy) may reveal specific features such as atrophy of the outer layer of the skin. Molecular genetic testing can confirm a diagnosis of AEC syndrome if they detect mutations in the TP63 gene known to cause the disorder. The condition shows an autosomal dominant pattern of transmission with 30% of patients having an affected parent, while 70% have a "*de novo*" TP63 pathogenetic variant[4].

The molecular basis of AEC syndrome has been shown mainly to involve heterozygous mutations in the sterile alpha motif (SAM) domain within the tail region of TP63 located on chromosome 3 (3q28). Atypical mutations include an intronic splice site mutation and a single amino acid insertion, but these also occur within the SAM domain. This region of TP63 is thought to be important in protein-protein interactions, for example in binding TP63 to the RNA splicing protein, apoptbec1 binding protein (ABBP1)[1,10].

TP63 is a homologue of the TP53 tumor suppressor gene, encoding for the p63 protein, a member of a family of transcription factors involved in regulating both proliferation and differentiation of the epidermal keratinocytes, as well as many other processes, including limb and facial development. It is also known that mutations in TP63 lead to skin erosions[1,10].

Mortality results from hydroelectrolyte imbalance due to fluid loss, anemia, secondary infection, and sepsis, so accurate, early diagnosis is essential. Prognosis is generally good, depending upon the early and

aggressive management of potentially life-threatening skin erosions, careful management of fluids and nutrition, and ongoing management of the multiple clinical manifestations noted in AEC syndrome[6].

The approach must therefore be multidisciplinary, and long-term follow-up should be assured, coordinating the efforts of a team of specialists such as pediatricians, dermatologists, ophthalmologists, dentists, audiologists, otolaryngologists, a geneticist, speech therapist, and other healthcare professionals that may need to plan an affected child's treatment systematically and comprehensively[4]. Prenatal and preimplantation genetic testing are options for future pregnancies if a pathogenic variant in TP63 has been identified in an affected family member[6].

Therapy is guided by the symptoms, correcting the cleft palate/cleft lip, promoting the integrity of the skin barrier with emollients, preventing trauma and, where erosions are present, avoiding superinfection, and accelerating the epidermization process. Genetic counseling and psychological support are recommended for the patient and family.

Authors' contribution

J. Sousa-Marques: Conception and design of the study, report, review or other type of work; Acquisition of data either from patients, research studies, or literature. Analysis or interpretation of data either from patients, research studies, or literature. Drafting the article. Critical review of the article for important intellectual content Final approval of the version to be published. Agreement to be accountable for the accuracy or integrity of the work. A.G. Oliveira: Acquisition of data either from patients, research studies, or literature. Analysis or interpretation of data either from patients, research studies, or literature. Drafting the article. Critical review of the article for important intellectual content. Final approval of the version to be published. Agreement to be accountable for the accuracy or integrity of the work. C. Gomes: Drafting the article. Critical review of the article for important intellectual content. Final approval of the version to be published. Agreement to be accountable for the accuracy or integrity of the work. S. Coelho: Drafting the article. Critical review of the article for important intellectual content. Final approval of the version to be published. Agreement to be accountable for the accuracy or integrity of the work. I. Andrade: Drafting the article. Critical review of the article for important intellectual content Final approval of the version to be published. Agreement to be accountable for the accuracy or integrity of the work.

Funding

None.

Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

References

1. Fete M, vanBokhoven H, Clements SE, McKeon F, Roop DR, Koster MI, et al. International Research Symposium on Ankyloblepharon-Ectodermal Defects-Cleft Lip/Palate (AEC) Syndrome. American Journal of Medical Genetics Part A. 2009 Sep;149A(9):1885-93.
2. Sutton VR, van Bokhoven H. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. TP63-related disorders. Seattle: University of Washington, Seattle; 2010. [updated 2021 Apr 1]. GeneReviews®. 1993-2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK43797/.
3. Tomková H, Fujimoto W, Uchida T, Macko J, Gaillyová R, Bucková H. AEC syndrome caused by heterozygous mutation in the SAM domain of p63 gene. Eur J Dermatol. 2010;20(3):411-3. https://doi.org/10.1684/ejd.2010.0931.
4. AEC Syndrome - National Organization for Rare Disorders [Internet]. rarediseases.org. [cited 2023 Feb 3]. Available from: https://rarediseases.org/rare-diseases/aec-syndrome/?filter=ovr-ds-resources.
5. Wright JT, Fete M, Schneider H, Zinser M, Koster MI, Clarke AJ, et al. Ectodermal dysplasias: Classification and organization by phenotype, genotype and molecular pathway. American Journal of Medical Genetics Part A [Internet]. 2019 Mar 1;179(3):442-7. Available from: https://pubmed.ncbi.nlm.nih.gov/30703280.
6. UpToDate [Internet]. www.uptodate.com. [cited 2023 Feb 22]. Available from: https://www.uptodate.com/contents/tumor-protein-p63-tp63-related-ectodermal-dysplasias?search=Tumor%20protein%20P63%20related%20disorders&source=search_result&selectedTitle=1~19&usage_type=default&display_rank=1#H41406352.
7. Cole P, Hatef DA, Kaufman Y, Magruder A, Bree A, Friedman E, et al. Facial clefting and oroauditory pathway manifestations in ankyloblepharon-ectodermal defects-cleft lip/palate (AEC) syndrome. American Journal of Medical Genetics Part A. 2009 Sep;149A(9):1910-5.
8. Zhang Z, Cheng R, Liang J, Lu Z, Wang Y, Li M, et al. Ankyloblepharon–ectodermal dysplasia–clefting syndrome misdiagnosed as epidermolysis bullosa and congenital ichthyosiform erythroderma: Case report and review of published work. The Journal of Dermatology. 2019 Feb 27;46(5):422-5.
9. Serra G, Antona V, Giuffré M, Li Pomi F, Lo Scalzo L, Piro E, et al. Novel missense mutation of the TP63 gene in a newborn with Hay-Wells/Ankyloblepharon-Ectodermal defects-Cleft lip/palate (AEC) syndrome: clinical report and follow-up. Italian Journal of Pediatrics. 2021 Sep 28;47(1).
10. Payne AS, Yan AC, Ilyas E, Li W, Seykora JT, Young TL, et al. Two Novel TP63 Mutations Associated With the Ankyloblepharon, Ectodermal Defects, and Cleft Lip and Palate Syndrome. Archives of Dermatology. 2005 Dec 1;141(12).