BLEPHAROPHIMOSIS-PTOSIS-EPICANTHUS INVERSUS SYNDROME

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SUMMARY

Purpose: To report the ocular phenotype of blepharophimosis-ptosis-epicanthus inversus syndrome (BPES).
Methods: Ophthalmological examination of a 36 year-old proband and detailed family history evaluation, including assessment of available facial photographs of affected relatives, was performed.
Results: There were four affected males and one female in three generations. The proband underwent two surgical eyelid procedures in childhood. Upon our examination, he had symmetrical ptosis with shorter eye lids, and incomplete medial canthal closure. The skin in the inner canthi was scarred, and the medial lower lids slightly everted, leading to malapposition of lacrimal punctae. There was no epicanthus inversus, however it was impossible to determine the status prior to the eyelid surgeries. The best corrected visual acuity was 0.66 and 0.33, in the right and left eye, respectively. The rest of the ocular examination was normal. There was no strabismus. Based on inspection of photographs taken prior to eyelid surgeries, the typical signs of BPES were also present in a son and a nephew of the proband. Photographs of the affected brother were not available, but family history indicated that he had BPES and underwent in his childhood two eye lid surgeries. Atypical ocular phenotype of the proband's mother has been published previously.
Conclusions: Ophthalmologists need to be aware about the phenotype of BPES, with the potential for visual impairment, and the need for personalized management in the affected families.

Key words: blepharophimosis-ptosis-epicanthus inversus, phenotype, *FOXL2*

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INTRODUCTION

Blepharophimosis-ptosis-epicanthus inversus syndrome (BPES; MIM #110100) is a rare autosomally dominant pathology with an estimated incidence of 1:50 000 (9, 14). The ocular finding is characterised by bilateral, congenital, mostly symmetrical ptosis with horizontal truncation of the ocular apertures. There is also present epicanthus inversus; a crescent shaped fold of the skin of the lower eyelid, which covers the inner canthus of the eye. The syndrome also frequently involves a lateral shift of the inner canthus with preservation of normal interpupillary distance (telecanthus) (3, 14).
Two types of BPES are differentiated. Type I, in addition to the ocular symptoms, is characterised by premature ovarian failure with extinction of the function of the ovaries before the 40th year. In type II the onset of the menopause is physiological (6, 17).
BPES originates upon the presence of a pathogenic mutation in the gene FOXL2 (MIM #605597), which is located on the long arm of the 3rd chromosome in the region of 3q23. It concerns a transcription factor on one coding exon. The protein FOXL2 has 376 amino acids, including 110 amino acids of the long "forkhead" DNA binding domain (3, 6). The ocular symptoms in BPES are generally without greater variability in the afflicted individuals, regardless of the type of pathogenic mutations (8).

OBJECTIVE

The objective of the article is to describe the ocular finding in members of a family with BPES.

METHODS

We performed an ocular examination on a 36 year old proband of Slovak origin, in whom we determined pathogenic mutation c.663_692dup (p.Ala225_Ala234dup) in the gene FOXL2 (7). We further conducted a detailed family anamnesis, including assessment for the presence of signs of the syndrome in first degree relatives on the basis of an evaluation of photographs of the face. All the documentation presented in this study has been published with the consent of the depicted family patients and their legal representatives.

RESULTS

BPES syndrome was unequivocally present in the family in four individuals of male sex: the proband, his son, the brother of the proband and the son of the brother of the proband. In all four males it was necessary to resolve the condition surgically in childhood. Upon a study of photographs we stated a mild form of the syndrome also in the mother of the proband, who stated that she had experienced the onset of menopau-

se at the age of around 45 years. On the basis of this information we determined that the condition in the family being studied concerns BPES type II. A detailed description of the ocular finding in the mother of the proband was published by the authors Krepelova et al. (11). Neither the parents nor the sister of the mother of the proband demonstrated any signs of the condition according to the available photographs.

The proband (fig. 1a) underwent two surgical procedures at the age of 3 and 6 years, his son (8 years) was operated on 3 times at the age of 3 months, 2 and 4 years, the brother of the proband (33 years) underwent two operations at the age of 3 and 5 years, and his son (4 years) underwent surgery during the course of the first year of life. All the operations were performed at different centres. The photographs of the son of the proband fig. 1b, c, d) and the son of the proband's brother after birth documented a typical finding for BPES; bilateral laterally symmetrical deformity of the lower eyelids with blepharophimosis, ptosis, epicanthus inversus and a obliterated orbito palpebral sulcus.

At our examination we determined symmetrical ptosis in the proband with truncated eyelids, in the nasal half with incomplete medial canthal closure. The skin in the inner canthi appeared to be scarred and the lower eyelids were slightly everted in the inner halves, so the lachrymal puncta did not adhere to the lachrymal lakes (fig. 2a). There was also present characteristic compensatory engagement of the musculus frontalis. Best corrected visual acuity in the right eye was 0.66 (6/9) s -2.5 D =-1,75 Dcyl ax 90° and in the left eye 0.66 (6/18) s -2,25 D = -0,75 Dcyl ax 90°. The remainder of the ocular finding was within the norm. There was no presence of strabismus.

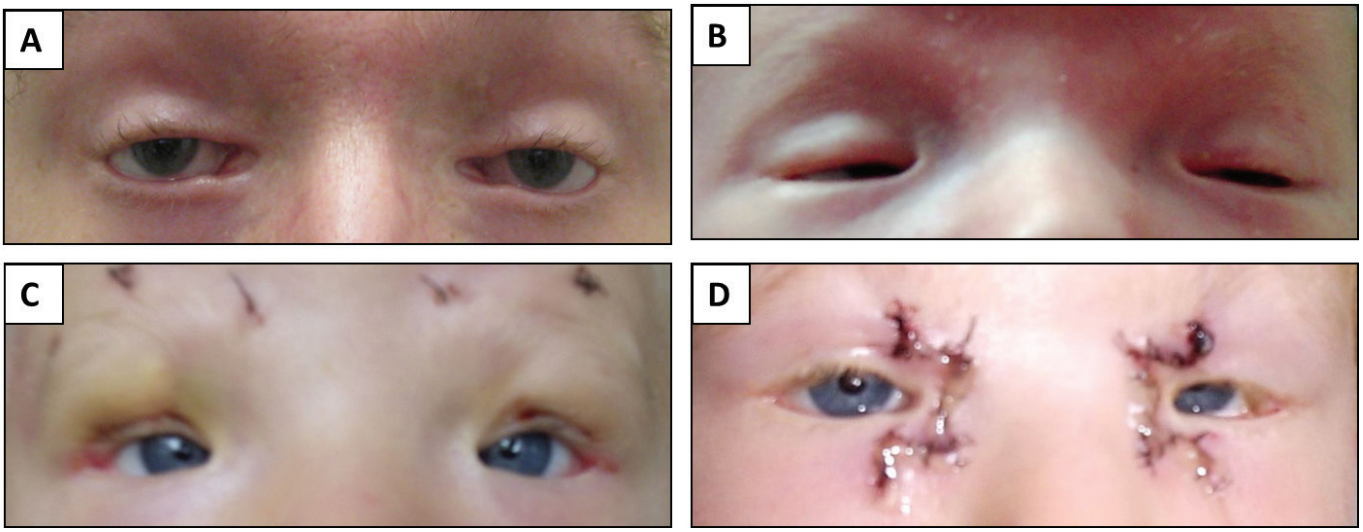
DISCUSSION

The article describes the clinical ocular finding in BPES syndrome, present in the family we examined. In the Czech and Slovak literature we found only a brief clinical description of a patient with this syndrome (15), without a further designated subtype or photographic documentation.

The pathology was documented in three consecutive generations, including transmission from father to son, which corresponds to autosomally dominant heredity characteristic of this syndrome. The determination of heterozygote mutation c.663_692dup30 in the gene FOXL2 confirmed the clinical diagnosis of BPES and autosomally dominant type of transmission (5).

Whilst the photographic documentation in the case of the son and nephew of the proband documented a characteristic finding for BPES, epicanthus inversus was not determined in the proband upon our examination. With regard to the surgical procedures which the patient had undergone, however, it is not possible to determine the original condition. Nevertheless, an interesting fact is that epicanthus inversus was also not present in the mother of the proband, who did not undergo any surgical procedures in the region of the eyelids (11). With regard to the fact that both the proband and his mother are carriers of a relatively frequent mutation, described in the literature in a number of families with typical BPES, i.e. including the presence of epicanthus, we are of the opinion that the origin of the slightly different clinical expression is in connection with the different genetic background (6).

In the proband we observed bilateral diminution of visual acuity, more pronounced in the left eye, which we attributed to amblyopia. Amblyopia is relatively frequent in the case of BPES, and may occur in connection with strabismus upon anisometropia or due to deprivation upon ptosis of the eyelids. For example, Beckengsal et al. (1) determined significant astigmatism in 40% of individuals in a cohort of 28 patients, whilst 64% had amblyopia together with strabismus, whilst amblyopia without strabismus was present in 24%.



Obr. 1. Photos of eyes and their surroundings of an individuals with the syndrome Blepharophimosis-ptosis-epicanthic fold inverzus, A) investigated proband, B), son of the proband at the age of 10 days, C), son of the proband at the age of 2 years after the second suspension surgery d) the son of the proband age 4 years after For years, double sculpture. Surgical procedures have been performed by the authors of this work.

Ocular treatment of BPES is surgical. Several procedures are performed as standard in multiple steps. It is necessary to consider the timing of the surgical intervention carefully with regard to the risk of occurrence of amblyopia, requiring timely solution, as against the advantages of a procedure at a later age, at which more reliable correction of ptosis and better cosmetic results are attained. It is recommended that the first procedure is performed before the age of 5 years, in order to minimise the psychological consequences in connection with school attendance (1). First of all medial canthoplasty is performed, in the second phase ptosis is adjusted. If the epicanthal fold is small, Y-V canthoplasty is performed, whereas more pronounced folds are corrected by Z canthoplasty. Telecanthus is corrected by truncation of the medial canthal tendon or its transnasal fixation (12). In smaller cohorts of patients a number of techniques for adjusting the condition within a single procedure have been described, the advantage of which resides in reducing the psychological and physical burden in connection with multiple operations under general anaesthesia and a shorter time for rehabilitation (2, 10, 13, 16).

The gene FOXL2 also plays a significant role in the development and function of ovaries, which is manifested in patients with BPES type I as premature ovarian failure (3). The mutation c.663_692dup30, determined in the family we studied, leads to a duplication by the size of 10 alanine residues (p.Ala225_Ala234dup), which causes an extension of the chain of this amino acid from 14 residues to 24. The sequential variants leading to polyalanine expansion form approximately one third of all intragenic mutations in FOXL2, and mostly cause only defects of the eyelids (5). In the family we studied also no further abnormalities were determined, including normal onset of menopause in the afflicted woman, documenting that this represents BPES type II (6). However, it is necessary to emphasise that in a number of female patients with detected polyalanine expansion malfunctions of the ovaries have been describe, and the hypothesis has been forwarded that ovarian failure may occur at a later age. With advancing age, carriers of the mutation thus have a lower chance of becoming pregnant in comparison with normal women (3). As a result a professional examination is recommended for female patients, with reference to assessment of ovarian functions (3).

Mutations in the gene FOXL2 occur in up to 50 % of cases de novo, meaning that parents without signs of the pathology produce offspring with an ocular phenotype characteristic of BPES, which may lead to perplexities in diagnosis. In this case, however, it is not possible to determine the type of BPES according to the anamnestic data from women after menopause. The determination of a causal mutation may thus be of great significance in providing consultancy and prognosis with regard to the potential occurrence of premature ovarian failure in afflicted daughters.

Because neither of the parents of the proband manifested signs of BPES, we are of the opinion that here also the pathogenic change occurred de novo, as a consequence of a mutation in the embryonic cell or mosaicism in one of their parents (grandparents of the proband on the maternal side) (3, 4).

BPES manifests virtually 100% penetration for the ocular phenotype, specifically in type I 100% is stated, and in type II 96.5% (17). It is therefore improbable that daughters of afflicted men without clinical symptoms of the disease would inherit the pathogenic variant in FOXL2. Following an agreement with the parents and in accordance with the ethical regulations, the daughters were given the option of deciding whether they wished to be tested for the presence of determined pathogenic change in adulthood.

With regard to affliction of the function of the ovaries in certain women and the psychological burden in connection with different appearance and operations in childhood age, BPES syndrome is considered sufficiently serious that if the afflicted individual so wishes, pre-implantation diagnosis is performed for this indication (7).

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