

Novel occurrence of Axenfeld-Rieger syndrome in a patient with blepharophimosis ptosis epicanthus inversus syndrome

Glaucoma and Cornea Services, Dr. Rajendra Prasad Centre for Ophthalmic Sciences, ¹Department of Anatomy, All India Institute of Medical Sciences, New Delhi, India

Correspondence to: Dr. Tanuj Dada, Dr. Rajendra Prasad Centre for Ophthalmic Sciences, All India Institute of Medical Sciences, New Delhi – 110 029, India. E-mail: tanujdada@gmail.com

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Bhavin M Shah, Tanuj Dada, Anita Panda, Mukesh Tanwar¹, Shibal Bhartiya, Rima Dada¹

Blepharophimosis ptosis epicanthus inversus syndrome (BPES)

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is a complex eyelid malformation characterized by the classical tetrad of blepharophimosis, telecanthus, ptosis, and epicanthus inversus. It has been reported to be associated with other ocular anomalies such as euryblepharon, strabismus, nystagmus, amblyopia, microphthalmos, lacrimal drainage apparatus abnormality, extra ocular muscle abnormalities, microcornea, trabecular dysgenesis, optic nerve hypoplasias, and colobomas of the optic disk. We describe a case of BPES with Axenfeld–Rieger syndrome, a neurocristopathy characterized by maldevelopment of the anterior segment with predisposition to development of glaucoma. Interestingly, both syndromes are caused by mutations in the same class of genes, namely the winged-helix/forked transcription factors (*FOX*) involved in a variety of developmental processes.

Key words: Axenfeld-Rieger Syndrome, anterior segment dysgenesis, blepharophimosis ptosis epicanthus inversus syndrome, glaucoma

Blepharophimosis ptosis epicanthus inversus syndrome (BPES) is a rare genetic disorder occurring either sporadically or as an autosomal dominant disorder. Patients with BPES have a combination of congenital anomalies of the eyelids characterized by reduction of horizontal fissure length, congenital ptosis, epicanthus inversus, and telecanthus.^[1] BPES is reported to be caused by mutation in the *FOXL2* gene on chromosome 3q23 and recently also by mutation in the region of chromosome 7p13–p21.^[2,3] Axenfeld–Rieger Syndrome (ARS), on the other hand, represents the spectrum of anterior segment developmental abnormalities that include angle anomalies such as prominent anteriorly displaced Schwalbe’s line, iridocorneal tissue strands with high insertion of iris into the posterior trabecular meshwork, iris abnormalities including corectopia, iris atrophy, iris hole with or without systemic abnormalities.^[4] Genetic analysis in patients with ARS has identified three distinct loci at chromosome 4q25, 6p25, and 13q14. The genes at the first two loci have been identified as *PITX2* and *FOXC1* respectively.^[5] Recently we examined a patient of BPES who also had findings consistent with ARS. The novel simultaneous occurrence of these two syndromes has not been reported in the literature till date.



Figure 1: Clinical photograph showing bilateral blepharophimosis, epicanthus inversus, and ptosis with frontalis overaction

Case Report

A 20-year-old male patient presented in our out-patient department with chief complaint of drooping of both the upper lids since birth. There was no history of consanguineous marriage of parents and no family history was found of any syndrome in parents or siblings. A comprehensive ophthalmic and systemic examination was performed. The patient had a refractive error of -1.5DS/-0.5 DC @ 180° in each eye and the best corrected visual acuity was 20/40 in both the eyes. There was no facial asymmetry; however, flattening of the mid face and synophresis were present. There was bilateral severe ptosis (left > right) with frontalis muscle overaction only on the right side. The upper lid crease and the levator palpebrae superioris function were absent on both the sides with a good Bells phenomenon. The horizontal palpebral apertures measured 25 mm in both the eyes with the vertical apertures being 4 mm and 0 mm respectively. The patient had a telecanthus with the intercanthal distance being 35 mm with an interpupillary distance of 60 mm. The outer canthal distance was 85 mm. Eyelid examination revealed bilateral epicanthus inversus [Fig. 1].

Slit lamp examination revealed corectopia with iris hole in the right eye. Gonioscopically, the features were similar in both the eyes and included a prominent anteriorly shifted Schwalbe’s line with prominent iridocorneal tissue strands, anterior insertion of the iris, and a few broad based peripheral anterior synechiae [Fig. 2]. The intraocular pressures were 18 and 20 mm of Hg respectively with the Goldmann applanation tonometry. Fundus examination revealed a vertically oval optic disk with 0.2 cups and sharp foveal reflex in both the eyes. Visual field examinations with the Humphrey 30-2 SITA Standard protocol did not reveal any glaucomatous changes. Systemic examination was unremarkable except for mild mental retardation (IQ range: 62-66). PCR-based mutation detection of the *PITX2* gene showed the absence of any mutations in all exons and promoter region in proband and siblings, suggesting that other loci may be responsible for the phenotype.

Discussion

Since its original description by Vignes,^[6] BPES has been

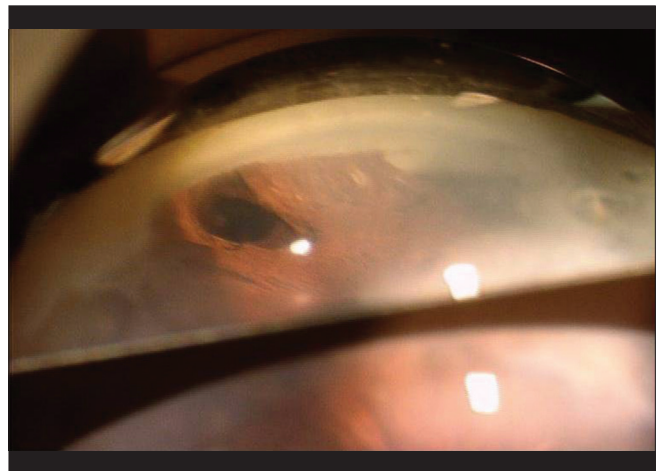


Figure 2: Goniophotograph showing a prominent Schwalbe’s line with peripheral broad based anterior synechiae and iris hole

reported to be associated with other ocular anomalies such as euryblepharon, strabismus, nystagmus, amblyopia, microphthalmos, microcornea, lacrimal drainage apparatus abnormality, extra ocular muscle abnormalities, and colobomas of the optic disc.^[1,6,7] Chismire and Witkop also reported associated trabecular dysgenesis with anterior insertion of iris and optic nerve hypoplasia in a patient with BPES.^[8] The patient however had a normal Schwalbe's line with absence of any iridocorneal tissue strands or any iris abnormalities characteristic of ARS.

ARS, a "neurocristopathy," is caused by a maldevelopment of neural crest cells causing characteristic anterior segment abnormalities.^[2] Glaucoma, developing in more than half the cases of ARS, usually presents in childhood or young adulthood. The patho-mechanism of glaucoma appears to be due to incomplete maturation of the trabecular meshwork and Schlemm's canal.^[9]

Although BPES and ARS have been well described in the literature, their simultaneous occurrence in a patient has never been described before. Our patient had all the classical eyelid manifestation of BPES and also the characteristic iris and gonioscopic findings of ARS, though fortunately there was no evidence of any glaucomatous damage. The two syndromes are distinctly different in their clinical presentation, associations and also in the locus of genetic mutations. Moreover, despite the fact that both the syndromes are caused by mutation in the same class of genes, namely the winged-helix/forked transcription factors, the locus of genetic mutation is distinct for each of them. These genes are involved in variety of developmental process in the body. However no mutation was detected in either the promoter or coding/noncoding region of the PITX2 gene.

Studies have shown that other genes may also be responsible for anterior segment dysgenesis. Recently PAX6 and MAF genes have been shown to cause anterior segment dysgenesis. Mutation of PAX6 (located on 11p13) has been reported in an isolated case of ARS.^[10,11] Another study has reported that mutations in MAF (transcription factor gene on 16q33.2) gene may lead to corneal opacity, cataract, microcornea, iris coloboma, and anterior segment dysgenesis.^[12] During embryonic eye development, MAF is expressed in surface ectodermal component of lens placode and vesicle.^[13] So a lens-specific signaling malformation may lead to blocking anterior chamber formation during development of eye. And it has been suggested that lens epithelium generates signals which are required for induction of corneal endothelium. Thus lens-cornea signaling may account for ARS.

Thus, this case report is unique in reporting the simultaneous occurrence of these two genotypically and phenotypically distinct syndromes. The importance of this novel association lies in early identification of angle abnormalities in patients with BPES which

may predispose these patients to development of glaucoma. As glaucoma may manifest only in late childhood or even adulthood, these patients must be closely followed up for glaucoma even after they have been managed for the correction of eyelid abnormalities of BPES in order to prevent irreversible sight-threatening damage secondary to glaucomatous optic neuropathy.

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