A rare association of aniridia with conjunctival xerosis in two Indian siblings with PAX6 mutation

Dear Editor,

PAX6 encodes a paired homeodomain transcription factor that plays a vital role in eye and neural development. Its expression is initially found in the anterior neural plate and later on in the lens field of the head surface ectoderm and optic pit.[1] PAX6 heterozygous gene mutations have been known to cause aniridia, while homozygous mutation is associated with severe brain abnormalities, microencephaly, and early postnatal death with the absence of eye and nose in humans and rodents.[2,3] In the present study, we screened mutation in PAX6 gene in an Indian family with aniridia and a broad range of ocular malformations.

The case described here is a one and half year old baby girl having multiple ocular complications including bilateral aniridia, microcornea, glaucoma, subluxated lens with no evidence of cataract, high myopia, and conjunctival xerosis [Fig. 1a]. After obtaining the history of patient, a comprehensive ophthalmic examination of anterior and posterior segments was performed. The pupils were dilated using a combination drop of 0.2% cyclopentolate with 1% phenylephrine (Cyclomydril) approximately 15 min before examination. A few examinations were performed under general anesthesia where non-compliance of patient was expected. Visual acuity was evaluated using Teller’s acuity card test[4] at a distance of 55 cm. Refraction was performed using cycloplegic retinoscopy. Cover test was performed to assess the binocular vision and ocular motility. Mean intraocular pressure (IOP) was measured with hand-held Perkin’s applanation tonometer. Red reflex test was performed to evaluate tear film, cornea, aqueous humor, lens, and vitreous humor. The patient had visual acuity of 26 cycle/degree equivalent to 20/24 of Snellen’s Scale in both eyes. The mean refractive error was −4.00 diopters (D) in both eyes, and mean horizontal corneal diameter was 7.5 mm and 8.0 mm in the right and left eyes, respectively. The axial length of right and left eyes were 26.55 mm and 27.24 mm, respectively. Mean intraocular pressure (IOP) was 24 mm Hg in both eyes. The optic cup/disc ratio was not measured and the posterior segment analysis showed myopic fundus.

The patient was prescribed vitamin A (2,00,000 Units) supplementation for the management of conjunctival xerosis till the age of 5 years. Medical records and oral information from the parents revealed that the patient’s elder brother also had complex ocular conditions including aniridia, microcornea, glaucoma, subluxated lens, and conjunctival xerosis, while her mother had aniridia and glaucoma, and the father is blind since birth. The family pedigree is shown in Fig. 1b.

Written informed consent was obtained from the parents of the proband. Genetic analysis of the PAX6 gene using polymerase chain reaction and Sanger sequencing was carried out. All the study procedures were conducted in accordance with the tenets of the Declaration of Helsinki and were approved by the Institutional Ethical Committee. Genetic investigations revealed a heterozygous mutation (c.781C>T) in the PAX6 gene in the patient, her brother, and mother, and not in her father. This mutation is present in exon-10 and was found to cause premature termination of PAX6 protein (p. Arg261Ter) that results in the loss of a partial homeodomain and the entire PST (Proline-Serine-Threonine) domain. In silico analyses showed that this mutation is potentially deleterious to the protein function. The PAX6 transcript containing the premature termination mutation (p.Arg261Ter) is believed to undergo nonsense-mediated decay and loss of protein level by 50% that leads to haploinsufficiency and aniridia.[5-7]

Although the PAX6 mutation (p.Arg261Ter) have been reported in few other population,[8-10] this is the first report from India where this mutation is associated with a broad range of ocular anomalies. To the best of our knowledge, this is the first study to report the association of conjunctival xerosis with aniridia in patients with PAX6 mutation.

 Conjunctival xerosis is a disease associated with vitamin A (retinoic acid) deficiency or insufficiency.[11] A study by Shetti and Patil [1996] showed resolution of Bitot’s spot and conjunctival xerosis upon vitamin A supplementation within a month of treatment in a case with aniridia along with conjunctival xerosis and Wilm’s tumor.[12] CYP26B1, a retinoic acid metabolizing enzyme is a downstream target of the PAX6 gene.[13] Therefore; we hypothesize that the presence of conjunctival xerosis in this family with PAX6 mutation might be owing to the inability of the mutant PAX6 to transactivate Cyp26b1 and subsequent failure in retinoic acid metabolism.
However, the involvement of other proteins and enzymes responsible for vitamin A binding, transportation, and metabolism could also be considered. Further, in vitro and in vivo experiments are warranted to confirm this hypothesis.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

Nair Vidya Gopinathan¹, Sankaranaranayanan Rajkumar¹,², Abhay Raghukant Vasavada¹

¹Department of Pediatric Ophthalmology, Iladevi Cataract and IOL Research Centre, Ahmedabad, Gujarat, ²Department of Ophthalmic Genetics, Aditya Jyot Foundation for Twinkling Little Eyes, Mumbai, Maharashtra, India

Correspondence to: Dr. Sankaranaranayanan Rajkumar, Department of Ophthalmic Genetics, Aditya Jyot Foundation for Twinkling Little Eyes, Mumbai - 400 031, Maharashtra, India. E-mail: srajkumar31@gmail.com

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Dear Editor,

Discontinuing topical prostaglandin analogues (PGAs) on account of their systemic side effects is rare in clinical practice. [1] Presented series details three cases started on topical PGAs who communicated gastric and cardiac complaints within few days of treatment initiation.

Case 1
A 48-year-old male diagnosed as primary open-angle glaucoma, was started on timolol and latanoprost eye drops. After 7 days, patient reported gastric burning. He was given antacids. Patient reviewed after 3 weeks and stated that he has stopped both eye drops for past 2 weeks and has no gastric complaints. Patient was counselled and started on timolol and dorzolamide eye drops. Unmasked rechallenge with latanoprost and bimatoprost eye drop on a later date, made the patient report gastric symptoms each time.

Case 2
A 60-year-old female with primary open-angle glaucoma was started on latanoprost eye drop. In a week, she complained of worsening of pre-existing gastric acidity, vomiting and loss of appetite. Referral to physician revealed normal investigations. She was switched to dorzolamide eye drop. No major gastric complaints have been reported thereafter.

Case 3
A 68-year-old otorhinolaryngologist, diagnosed as primary angle closure glaucoma in both eyes at a tertiary eye hospital, was started on pilocarpine and latanoprost eye drops. Within 1 month, he reported episodes of angina. He had recurrent palpitations for 1 year. During this period, he reviewed three times at the eye institute. He was investigated at cardiac unit and got treated for vasospastic angina. The subject, being a medical professional, did a literature search and stopped latanoprost eye drop on this own. Subsequently, as stated, he never had palpitations or angina.

It is speculated that stimulation of the smooth muscles and visceral nociceptors combined with vasoconstriction by Prostaglandin F2α are responsible for the gastriointestinal and cardiac effects. [2-5] Ophthalmologists need to be aware of such unfamiliar systemic effects of topical PGAs and exercise caution while usage in susceptible subjects.

Declaration of patient consent
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Conflicts of interest
There are no conflicts of interest.

Lipi Chakrabarty
Department of Ophthalmology, Chandulal Chandrakar Memorial Medical College and Hospital, Durg, Chhattisgarh, India
Correspondence to: Dr Lipi Chakrabarty, Department of Ophthalmology, CCM Medical College, Kachandur, Durg-490024, Chhattisgarh, India.
E-mail: dr.lipi@gmail.com

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