Pomeranian J Life Sci 2022;68(3):54-58 doi: 10.21164/pomjlifesci.838

Malformations of the anterior segment of the eyeball with microphthalmos in the contralateral eye in a child with the *PAX6* gene mutation – case report

Monika Modrzejewska[1, A] ✉, Wiktoria Bosy[2, B], Patrycja Woźniak[3, C]

[1] Pomeranian Medical University in Szczecin, II Department of Ophthalmology, Powstańców Wlkp. 72, 70-111 Szczecin, Poland
[2] Pomeranian Medical University in Szczecin, Scientific Association of Students II Department of Ophthalmology, Powstańców Wlkp. 72, 70-111 Szczecin, Poland
[3] Poznań University of Medical Sciences, I Department of Cardiology, Długa 1/2, 61-848 Poznań, Poland

[A] ORCID: 0000-0002-9221-8909; [B] ORCID: 0000-0002-9922-8165; [C] ORCID: 0000-0002-0833-6196

✉ monika_modrzej@op.pl

ABSTRACT

Introduction: The aim of this article is to present a congenital ophthalmic defect with microphthalmos in the contralateral eye and discuss causative factors with emphasis on limited treatment options of this genetic anomaly, which is responsible for approx. 10% of causes of innate blindness in pediatric patients.

Materials and methods: Clinical presentation of a 1-year-old child with diagnosed mesodermal disgenesis of the cornea in both eyes, with concomitant microphthalmos, optic nerve hypoplasia, and persistent hyperplastic primary vitreous in the left eye, treated with epikeratoprosthesis. Aniridia and buphthalmos of the right eye.

Results: Following the thorough diagnostic process of microphthalmos, the deletion *PAX6* gene mutation, as well as congenital heart defect (atrial septum defect type II and patent foramen ovale ASD II/PFO), were confirmed. Other abnormalities were excluded. Furthermore, the interstitial heterozygous deletion of exons 8, 9, and 10 in the 11p13 exon of the *PAX6* gene was confirmed in mother of a child. During pregnancy, the mother was suffering from hypothyroidism as well.

Conclusions: Continous ophthalmic screening in newborns and infants are of utmost importance in the early detection of congenital malformations of an eyeball. Despite being fairly common in comparison to other innate eyeball anomalies, microphthalmos remains a challenge in successful treatment focused on the improvement of vision. Due to the common co-occurrence of microphthalmos or anophthalmos and craniofacial abnormalities or axial skeleton defects, a crucial role is played by the cooperation between ophthalmologists and other pediatric specialists, including geneticists.

Keywords: microphthalmos; anophthalmos; aniridia; deletion of the *PAX6* gene; congenital eyeball malformations.

INTRODUCTION

Microphthalmos is a congenital malformation of the eyeball, and it defines unilateral or bilateral abnormalities of the eyeballs. The pathogenesis of microphthalmos (or anophthalmus) is associated with the disturbance of optic vesicle embryo development [1], although the exact pathological mechanism behind this anomaly remains unknown. It is suggested that genetic, prenatal, and maternal factors might contribute to the disturbed development of the eyeball.

The diagnosis of microphthalmos should be taken under consideration, if mean eyeball axial length or eyeball diameter is more than 2 standard deviations below the normal range of respective age groups [2]. According to the International Clearinghouse for Birth Defects Monitoring Systems, the corneal measurement <10 mm and anterolateral eyeball measurement <20 mm is highly suggestive of microphthalmos [3] and it can occur either unilaterally or bilaterally [4]. The prevalence rate is estimated 10/100 000 according to a European study [5], whereas an American study estimates the incidence of microphthalmos at 30/100 000 [6]. According to worldwide data, microphthalmos and anophthalmos concomitantly are responsible for approx. 10% of total amaurotic pediatric patients and are simultaneously 1 of the 5 most common causes of serious vision defects in Sweden [7]. It has also been proven that microphthalmos is correlated with 79% of other congenital defects such as craniofacial abnormalities or axial skeleton defects [8]. Etiopathogenetic factors, among many others, include prenatal variables (woman's age at the 1st and subsequent pregnancies, drugs abuse, infections during pregnancy), which further increase chances of microphthalmia.

Both influenza and the common cold virus pose a great risk during pregnancy [9]. Latest reports suggest that the infection with SARS-CoV-2 in 5/6th week of pregnancy causes severe congenital defects, such as unilateral microphthalmia, optic nerve hypoplasia, and retinopathy [10]. Among maternal factors, gestational diabetes mellitus is the most common [2]. Mouse genetic research indicated that serum hyperglycemia causes down-regulation of dishevelled-associated activator of morphogenesis 1 (Daam1) factor, which plays a crucial role in cytoskeleton reorganization process and is expressed in the development of an eye, the neural tube, and the heart. Hyperglycemia during pregnancy might result in eyeball development disturbances and it may eventually lead to microphthalmos [11].

The complex etiology of microphthalmia and anophthalmia include chromosomal anomalies including aneuploidy, triploid

syndrome, duplications, deletions, and translocations. Concomitantly, they account for approx. 20–30% of all microphthalmos cases, whilst the rest is caused by monogenic mutations such as nonsense, missense, insertions, deletions and splice-site mutations. The aforementioned mutations severely affect various genes, such as *SOX2*, *PAX6*, *RAX*, *OTX2* and *CHX10*, which are responsible for the pathogenesis of microphthalmos, and play a crucial role in the formation of the eye. *STRA6*, *ALDH1A3*, and *RARβ* genes are also worth mentioning, as they are involved in the retinoic acid signaling pathway [12]. Other congenital syndromes associated with microphthalmia include fetal alcohol syndrome, branchio-oculo-facial syndrome, Aicardy syndrome, CHARGE syndrome, Gorlin–Golz syndrome, Meckel syndrome, MIDAS syndrome (microphthalmia, dermal aplasia, and sclerocornea), isolated microphthalmia 7, Goldenhar syndrome, oculo-facio-cardio-dental syndrome, Walker–Waburg syndrome [13], as well as trisomy of distal chromosome 6p fragment [14]. In this article, the authors present a rare case of a 1-year-old child with a confirmed mutation in the *PAX6* gene. In the available PubMed literature, there are only 15 articles available on congenital ocular defects and deletion of the *PAX6* gene, and 53 articles on microptalm and 0 anopthalmic results. The authors emphasize the wide coexistence of congenital eyeball defects with other multiorgan abnormalities and limited therapeutic methods. The authors also underline the influence of causative factors on the pathogenesis of these abnormalities.

CASE REPORT

This case report presents a case of a 1-year-old child, delivered spontaneously (vaginal delivery) at 41 weeks. Infant's birth weight was 2838 g (Apgar 9, 9, 10, 10). The occurrence of any infection, exposure to chemical substances, and administration of potentially teratogenic drugs (except for levothyroxine because of hypothyroidism) during pregnancy were excluded. The family history was negative for any congenital birth defects. After the birth, the congenital eyeball defects i.e., mesodermal dysgenesis of the cornea of the right eye and microphthalmos of the left eye, were confirmed.

On the 4th day after the delivery, the multiorgan anomalies were also excluded. The laboratory tests results confirmed neither toxoplasmosis, rubella cytomegalovirus, herpes simplex, and HIV nor other metabolic diseases. The inflammatory parameters were within the normal range. The acylocarnitine, urine organic acids (GCSM) and transferrin isoform (CDG) profile were also within the normal range. Both laryngological and neurological examinations did not reveal any other abnormalities. The echocardiographical evaluation revealed atrial septum defect type II and patent foramen ovale ASD II/PFO, whereas the genetic tests confirmed *PAX6* gene deletion. Furthermore, the interstitial heterozygous deletion of exons 8, 9, and 10 in the 11p13(31815289_31819746) exon of the *PAX6* gene was confirmed by MALP genotype analysis technique in the child's mother.

Ten months after the delivery the RETCAM ophthalmic examination was carried out. The examination confirmed the mesodermal dysgenesis of the right eye, presented as peripheral and paracentral corneal haze, with a concomitant clear area of the central 1/3 part as well as a hazy temporal view of the eye fundus (Fig. 1). The aniridia of the right eye was also manifested with intraocular pressure ab 33 mmHg (above the normal range). The aforementioned phenomenons indicated retinochoroidal atrophy of the temporal side of the fundus (magnitude of 2–3 fundi) with tortuous retinal vessels. The examination of the right optic nerve did not reveal any significant abnormalities. The assessment of the retina of the contralateral eye was not visualizable. In the left orbital socket there was a vestigial eyeball with a degenerate anterior segment, covered with a conjunctiva (Fig. 2, 3).

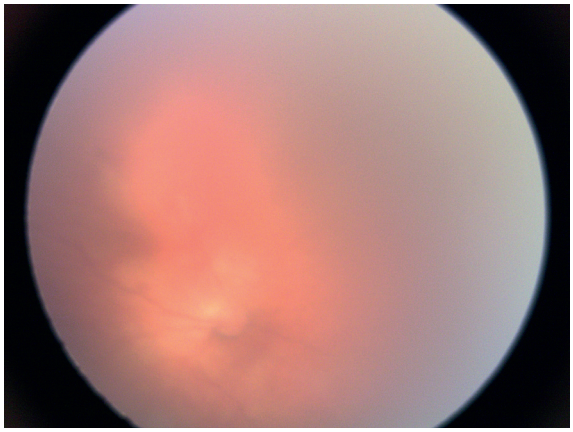

FIGURE 1. Photograph of the fundus from the right eye. Degenerative changes in the retina from the temporal disc of the optic nerve with a tortuous course of venous vessels. The left eyeball-fundus of the eye was impossible to assess

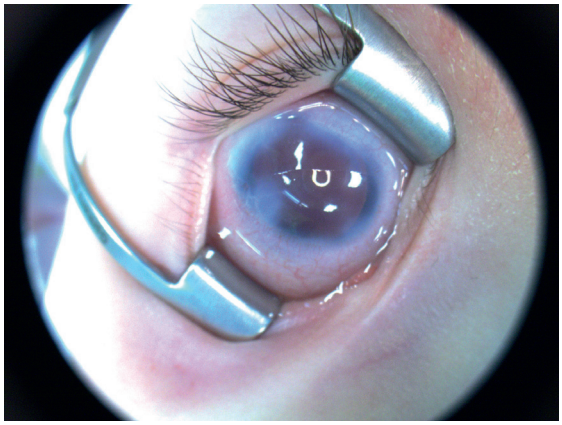

FIGURE 2. Photography of the anterior segment of the eyeball of the right eye of a child with microphthalmos

Ultrasonography revealed shortened axial length of the right eyeball down up to 18 mm, degenerative lesions in vitreus, manifested as hypoechogenic cysts with hyperplastic mass, which was probably the patent primal vitreous humor. The space between the sheaths of the optic nerve, measured 3 mm beyond the posterior pole of the optic nerve, was 5.22 mm wide. Ultrasonography of the left eyeball depicted an axis length of approx. 7 mm, a hypogenic, unaffected eyeball, and the anatomical appearance of the retina. The left optic nerve diameter was 1.22 mm, indicating optic nerve hypoplasia.

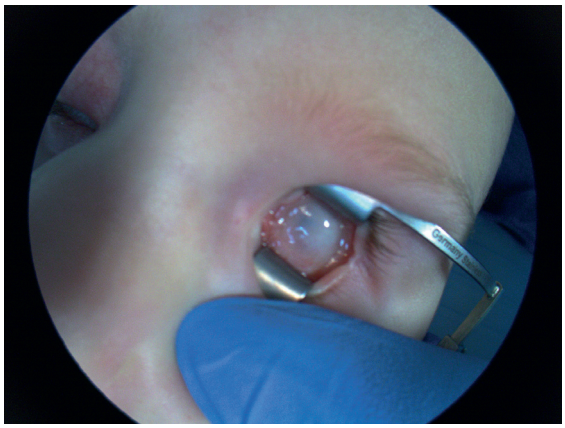

FIGURE 3. The eyeball of the left eye. A vestigial eyeball with degenerated front segment, covered with the conjunctiva

Magnetic resonance imaging (MRI) of the central nervous system did not reveal any abnormalities. The MRI of the orbital cavities confirmed uninterrupted trajectory of the optic nerve and unaffected optic chiasm (Fig. 4), along with left eyeball aplasia and a persistent hyperplastic primary vitreous in the left eye (linear, with less signal strength, approx. 2 mm long), treated with epikeratoprosthesis.

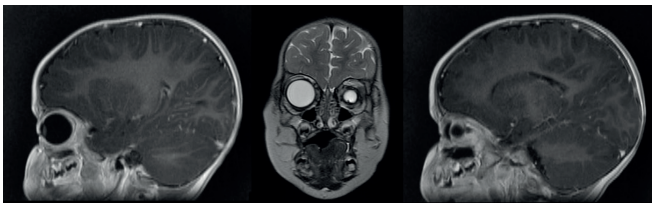

FIGURE 4. The magnetic resonance imaging of the orbital cavities. The uninterrupted trajectory of the optic nerve and unaffected optic chiasm, along with left eyeball aplasia and a persistent hyperplastic primary vitreous in the left eye (linear, with less signal strength tissue approx. 2 mm long), treated with epikeratoprosthesis

Flash visual evoked responses (FVER) electrophysiological examination demonstrated the normal latency of the P2 wave in the right eye, along with the complete lack of this wave in the left eye (Fig. 5). Electroretinography (ERG) examination revealed the bioelectric disturbance of the rod and cone cells in the right eye (Fig. 6). The complete lack of rod and cone cells response in the left eye.

The microphthalmos of the described child patient was treated with precisely designed epikeratoprosthesis in the left eye. Raised intraocular pressure in the right eye was treated with latanoprost (use once a day).

DISCUSSION

Microphthalmos is a fairly often diagnosed congenital eyeball anomaly among pediatric patients, along with other birth defects [8]. It is worth mentioning, that microphthalmos is not an isolated malformation, but is rather a part of the syndrome of symptoms of other multiorgan diseases [13, 15, 16].

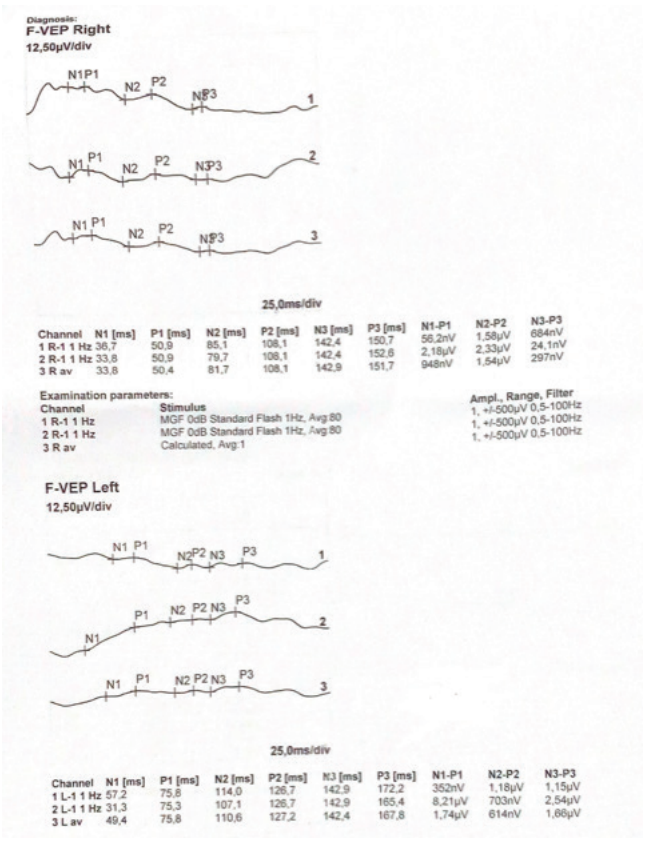

FIGURE 5. Flash visual evoked responses (FVER) examination. The normal latency of the P2 wave in the right eye, along with the complete lack of the wave in the left eye

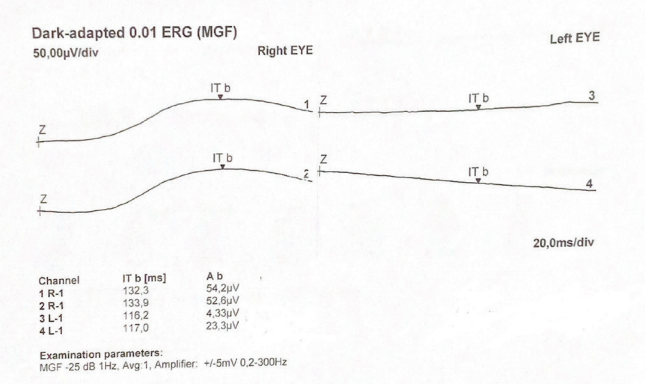

FIGURE 6. Electroretinography (ERG) test. Disruption of the bioelectrical function of the cone and rod system in the right eyeball. There are no rod and cone responses in the left eyeball

This case report describes the occurrence of microphthalmos along with mesodermal dysgenesis of the cornea, aniridia complicated with anophthalmus in the right eye. This birth defect coexists with *PAX6* gene deletion which leads to abnormal cell proliferation, differentiation as well as improper development of the eyeball, brain, pituitary gland, and pancreas. *PAX6* gene mutation is associated with the disturbance of the development of iris, retina, macula flava, and optic nerve, which further leads to nystagmus, as an effect of a serious vision impairment. Aniridia often causes and coexists with cataracts, glaucoma, and aniridia-associated keratopathy. Other ophthalmic symptoms such as central serous chorioretinopathy, serous macular detachment, papillomacular hold, high hyperopia, and

linear skin defects syndrome or MIDAS syndrome are also described [17]. Many studies have shown that children who have been diagnosed with anophthalmia or microphthalmia have different forms of visual impairment which lead to the most severe degrees of blindness. Electrophysiological tests such as FVER and ERG are used for diagnostics in this area, which is confirmed, among others, by Fahnehjelm et al. [7]. Blindness or significantly reduced amplitudes of visual potentials in the FVER test or disturbance of the functional function of retinal photoreceptors in the ERG test indicate a disturbance of the reaction to light in children with microphthalmos [18, 19]. Moreover, Churchill et al. described the same mutation present in Perthes anomaly, which predisposes to aniridia [18]. Perthes anomaly was suspected in the medical history of the child presented in this case report. This defect is associated with *PAX6* gene mutation, which is divided into 3 subtypes. Type I is characterized as central obfuscation of the cornea, along with synechia of the the iris and the cornea. Type II is described as central obfuscation of the cornea, along with cataracts or synechia of the cornea and the lens. Type III is manifested as Perthes type I or II anomaly, along with cleft palate and cheiloschisis, short stature, ear auricle malformation and mental retardation [19]. Katz et al. described co-occurrence of Perthes anomaly with microphthalmos, and persistent hyperplastic vitreous humor in the contralateral eye [20], which was confirmed in our pediatric patient as well. Furthermore, Brémond-Gignac et al. described the correlation of *PAX6* gene mutation and aniridia and buphthalmos [21].

In the article, the authors described the co-existence of micropthalmos of the 1 eye, along with aniridia, mesodermal dysgenesis and buphthalmos of the contralateral eye, which is associated with the aforementioned gene mutation. Furthermore, the echocardiographical evaluation revealed ASD II/PFO, which was confirmed by Modrzejewska et al. [15]. This study showed the co-ocurrence of microphthalmos and congenital heart defects. Along with *PAX6* mutation, mother's hypothyroidism was also a crucial causative factor of microphthalmos. Available studies confirm the correlation of thyroid insufficiency during pregnancy and eyeball neurogenesis disturbance (*PAX6* gene down-regulation and the deficiency of neuronal progenitor cells) [22, 23].

The contemporary option of treating microphthalmos is an individually designed epikeratoprosthesis, which improves the quality of life, appearance, and comfort. In the future, it might be possible to implant an eye prosthesis. Apart from the eyeball prosthesis, other part of protective eye machinery, for example eyelids (silicone or acrylic material), which offer durability and eyelashes retention with the use of autologous hair, can be used as an alternative for synthetic hair [24].

In their 22-year-long observational research on the microphthalmus treatment options, Gore et al. emphasize the beneficial effect of autologous dermis fat graft (DFG) as a new revolutionary method and an alternative to silicon implants of the orbital cavity. This is a promising method in regenerative treatment option of eyeball growth in the orbital cavity. The implants are sometimes used as a preliminary method before DFG, which improves the orbital cavity widening [25]. The alternative option is self-inflating hydrogel expansion, which according to Changal and Khandekar [26], as well as Hou et al. [27], expands the orbital cavity (88.8–91.8%) during the 2-year observation period, and provides satisfying functional and cosmetic effects [28].

SUMMARY

Microphthalmia is a serious congenital defect causing severe vision impairment and vision loss in children. One of the main treatment methods is the expansion of the orbital cavity with the use of epikeratoprosthesis, or hydrogel expander, as a preliminary procedure preceding the eyeball prosthesis. The autogenous DFG implantation into the orbital cavity might be a groundbreaking treatment method, which presented the most promising results in the latest study, when compared to currently widely used prostheses. The multidisciplinary screening, including genetic tests, plays a crucial role in the risk evaluation of congenital birth defects during the next pregnancy. The education of society concerning the exposure to toxic substances during pregnancy is of utmost importance in the prevention of congenital eyeball malformations, including microphthalmos and anophthalmus.

REFERENCES

1. Korniszewski L. Dziecko z zespołem wad wrodzonych: diagnostyka dysmorfologiczna. Warszawa: PZWL; 2005.
2. Gittens A, Gedrich M, Khandelwal M, Fischer R, Germaine P. Isolated presentation of congenital microphthalmia on fetal MRI. Radiol Case Rep 2019;14(9):1069-71. doi: 10.1016/j.radcr.2019.05.002.
3. Verma AS, Fitzpatric DR. Anophthalmia and microphthalmia. Orphanet J Rare Dis 2007;2:47. doi: 10.1186/1750-1172-2-47.
4. Benacerraf BR, Bromley BS, Jelin AC. Anophthalmia and Microphthalmia. Am J Obstet Gynecol 2019;221(5):B20-1.
5. Dharmasena A, Keenan T, Goldacre R, Hall N, Goldacre MJ. Trends over time in the incidence of congenital anophthalmia, microphthalmia and orbital malformation in England: database study. Br J Ophthalmol 2017;101(6):735-9.
6. Chambers TM, Agopian AJ, Lewis RA, Langlois PH, Danysh HE, Weber KA, et al. Epidemiology of anophthalmia and microphthalmia: prevalence and patterns in Texas, 1999–2009. Am J Med Genet A 2018;176(9):1810-8.
7. Fahnehjelm C, Dafgård Kopp E, Wincent J, Güven E, Nilsson M, Olsson M, et al. Anophthalmia and microphthalmia in children: associated ocular, somatic and genetic morbidities and quality of life. Ophthalmic Genet 2022;43(2):172-83.
8. Schraw JM, Benjamin RH, Scott DA, Brooks BP, Hufnagel RB, McLean SD, et al. A comprehensive assessment of co-occurring birth defects among infants with non-syndromic anophthalmia or microphthalmia. Ophthalmic Epidemiol 2021;28(5):428-35.
9. Li Y, Hou Z, Ding J, Cui Y, Qin B, Li D. Distinguishing risk factors between congenital anophthalmia and microphthalmia using multivariable logistic regression. Ann Transl Med 2020;8(11):704.
10. Morhart P, Mardin C, Rauh M, Jüngert J, Hammersen J, Kehl S, et al. Maternal SARS-CoV-2 infection during pregnancy: possible impact on the infant. Eur J Pediatr 2022;181(1):413-8.
11. López-Escobar B, Cano DA, Rojas A, de Felipe B, Palma F, Sánchez-Alcázar JA, et al. The effect of maternal diabetes on the Wnt-PCP pathway during embryogenesis as reflected in the developing mouse eye. Dis Model Mech 2015;8(2):157-68.

12. Dedushi K, Hyseni F, Musa J, Saliaj K, Vokshi V, Guy A, et al. A rare case of anophthalmia without any family history and antenatal risk factors. Radiol Case Rep 2021;16(12):3772-5.
13. Urban B, Bakunowicz-Łazarczyk A. Microphthalmos with concomitant giant eyball cyst – case report. Acta Ophthalmol 2006;108(7-9):337-9.
14. Lima Cunha D, Arno G, Corton M, Moosajee M. The spectrum of *PAX6* mutations and genotype-phenotype correlations in the eye. Genes (Basel) 2019;10(12):1050.
15. Modrzejewska M, Lachowicz E, Karczewicz D. Cases of congenital eye malformations in children. Ann Acad Med Stetin 2011;57(1):17-25.
16. Nishina S, Kurosaka D, Nishida Y, Kondo H, Kobayashi Y, Azuma N. Survey of microphthalmia in Japan. Jpn J Ophthalmol 2012;56(3):198-202.
17. Pedersen HR, Baraas RC, Landsend ECS, Utheim ØA, Utheim TP, Gilson SJ, et al. PAX6 Genotypic and Retinal Phenotypic Characterization in Congenital Aniridia. Invest Ophthalmol Vis Sci 2020;61(5):14. doi: 10.1167/iovs.61.5.14.
18. Churchill AJ, Booth AP, Anwar R, Markham AF. *PAX6* is normal in most cases of Peters' anomaly. Eye (Lond) 1998;12 (Pt 2):299-303.
19. Zaidman GW, Flanagan JK, Furey CC. Long-term visual prognosis in children after corneal transplant surgery for Peters anomaly type I. Am J Ophthalmol 2007;144(1):104-8.
20. Katz B, Enright J, Couch S, Harocopos G, Lee AR. Atypical presentation of Cat Eye Syndrome in an infant with Peters anomaly and microphthalmia with cyst. Ophthalmic Genet 2020;41(6):645-9.
21. Brémond-Gignac D. Le glaucome dans l'aniridie. J Fr Ophtalmol 2007;30(2):196-9.
22. Mohan V, Sinha RA, Pathak A, Rastogi L, Kumar P, Pal A, et al. Maternal thyroid hormone deficiency affects the fetal neocorticogenesis by reducing the proliferating pool, rate of neurogenesis and indirect neurogenesis. Exp Neurol 2012;237(2):477-88.
23. Thompson B, Davidson EA, Liu W, Nebert DW, Bruford EA, Zhao H, et al. Overview of PAX gene family: analysis of human tissue-specific variant expression and involvement in human disease. Hum Genet 2021;140(3):381-400.
24. Ruiters S, de Jong S, Mombaerts I. Bespoke ocular prostheses. Eye (Lond) 2019;33(7):1158-60.
25. Gore S, Grimaldi G, Mazzone G, Collin R, Savino G, Pagnoni M, et al. Treatment strategies and long-term outcomes in patients with congenital microphthalmia-anophthalmia with cyst. Br J Ophthalmol 2022;bjophthalmol-2020-318089.
26. Changal N, Khandekar RB. Eye conformers as socket expanders in children: experience at a Tertiary Eye Hospital in Central Saudi Arabia. Cureus 2021;13(2):e13465.
27. Hou Z, Xian J, Chang Q, Wei W, Li D. Digital evaluation of orbital development after self-inflating hydrogel expansion in Chinese children with congenital microphthalmia. J Plast Reconstr Aesthet Surg 2016;69(5):706-14.
28. Cui Y, Li Y, Hou Z, Wang Y, Chang Q, Xian J, et al. Management of congenital microphthalmos and anophthalmos with orbital cyst. J AAPOS 2019;23(2):92.e1-92.e6.