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POSTERIOR SEGMENT OPHTHALMIC MALFORMATIONS: HISTOPATHOLOGICAL SPECTRUM CORRELATED TO CLINICAL PRESENTATION AND REVIEW OF THE LITERATURE

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Abstract:

Purpose: *A wide range of posterior ophthalmic malformation is undervalued in the literature. This includes congenital cystic eye, microphthalmia and anophthalmia, Persistent Hyperplastic Primary Vitreous, and other retina disc anomalies. Moreover, there is a lack of regional data in the kingdom of Saudi Arabia regarding these anomalies. In this sense, the current study consists of a literature review and a case series of posterior ophthalmic malformation to see if there is any difference in the spectrum of pathology presentation in KSA compared to other regions.*

Methods: *Retrospective study reviewing medical records and histopathology finding looking for the spectrum of disease and presentation for patients with posterior ophthalmic malformations in King Abdulaziz University Hospital [KAUH] and King Khaled Eye Specialist Hospital [KKESH] from the period of [2000-2018].*

Results: *Total of seven out of twelve histopathologically confirmed cases of posterior ophthalmic malformation were included in this study. Charts revealed that most cases were females, and all of them presented unilateral anomalies. Family history, due to the high consanguinity rate in the studied population, revealed only one case of a patient with parents who were first degree relatives.*

Conclusion: *The current work adds a proper understanding of posterior ocular malformation pathological spectrum, together with the outcomes in KSA population to provide a better management and counseling.*

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INTRODUCTION:

A systematic interaction between the optic vesicle and the lens placode leads to the development of various structures of the eye of a vertebrate [1]. The optic vesicle is a lateral protrusion from the frontal section of the brain while the lens placode is an ectodermal structure that can reciprocate signals to the optic vesicle [2]. Characteristically, the crosstalk between the two structures leads to maturation of the optic vesicles into the adult retina while the lens placode develops into the structures of the anterior segment of the eye: popularly known as the lens and cornea [3]. Disturbances in the systematic development of the respective segments result in an array of posterior segment ophthalmic malformations such as the persistent hyperplastic primary vitreous [PHPV], congenital cystic eye, microphthalmia, anophthalmia, and morning glory disk anomaly, which may be attributed to genetic alterations and mutations.

Eye development starts as an evagination of the neural plate followed by the closure of the neural tube. The process is overly sophisticated, and any slight alterations of the controlling genes lead to structural malformations during the early stages of development. For instance, PAX6, SOX2, and OTX2 genes are critical during these development stages. Additionally, they are linked with brain development and regionalization [4]. The loss of The PAX6 gene exhibits multiple functions; however, homozygous loss of its functions leads to anophthalmia, brain malformations and/or neonatal death. The degree of malformations depends on the number of functions lost from the gene. Similarly, the homozygous loss of OTX2 and SOX2 functions leads to pre-implantation and malformations during the early stages of fetal development [5].

The current work reviews the most common posterior ocular malformations, and it analysis a case series of the mentioned anomalies in the Kingdom of Saudi Arabia.

Persistent Hyperplastic Primary Vitreous

Persistent hyperplastic primary vitreous [PHPV], also known as Persistent Fetal Vasculature [PFV], is an idiopathic group of complex ocular malformations caused by the incomplete apoptosis of the embryonic hyaloid vasculature [6]. The disorder induces the growth of a retrolental fibro-vascular mass that is often accompanied by cataract and microphthalmia [7], thus leading to visual defect in the affected eye. Nonetheless, PHPV is a disease spectrum that does not necessarily accompany severe morbidity or clinical effects [8] PHPV can be presented as anterior or posterior form, however, both forms are frequently observed, and it is usually presented unilaterally [9]. This group of anomalies is important because they are responsible for almost 5% of child blindness [10].

The embryogenesis of PHPV initiates with the formation of the hyaloid vascular system in the 4th to 5th week of gestation; this is the time when the hyaloid artery begins entry into the optic cup from the inferior end through the primitive dorsal ophthalmic artery. This is followed by its further entry anteriorly, eventually extending to the posterior pole of the lens [6]. The hyaloid artery is formed into the vitreous cavity by the vasa hyaloidea propria branches. A connection between the posterior aspect of this branching network and the choroidal vasculature forms the irido-hyaloid vessels [11]. Fundamentally, the hyaloid vascular system [HVS] in the primary vitreous provides nutrients for lens and retinal development [12]. Hence, whenever defects in the HVS regression occur, there is delayed maturation in the primary vitreous, which leads to the ocular disease [9]. This defect due to failure of regression of the primary vitreous after the first few prenatal weeks leaves a retrolental mass and causes other secondary defects such as cataract and the microphthalmia eye [13]. PHPV is typically present at full-term infants, where it can be identified at the time of birth in the majority of the cases.

PHPV is heterogeneous and complex in nature and its complete etiology has not been established [9], and is sometimes associated with various congenital syndromes, such as the morning glory disk anomaly [14]. Past research studies have identified a possible link between the PAX6 gene mutation and the resultant occurrence of PHPV. The study by Azuma et al [2003] discovered that mutations in the PAX6 gene were directly linked with the onset of PHPV in infants. In addition to PAX6, they also identified the negative role played by the PAX2 gene in deregulating the expression of the other gene, thereby causing mutations and potential occurrence of PHPV [15]. Mutations of the NDP gene have also been identified in some PHPV patients [16].

Although cataract and microphthalmia are the often-observed anomalies in PHPV cases, several abnormalities could be present as well, such as intravitreal hemorrhage, retinal detachment, glaucoma, and leukoria [17]. Like every other major disorder, PHPV can also be easily confused with several linked syndromes. To begin with, bilateral PHPV cases can be hard to differentiate from FEVR and Norrie disease [18]. Retinopathy of Prematurity [ROP], Coats' disease, microphthalmia, incontinential pigment, congenital cataract and ocular toxocariasis are some common diseases that are related to PHPV and may also be confused with it sometimes [13, 19, 20].

PHPV management begins at the initial detection of

the disease at the time of birth [8]. A vast majority of the PHPV cases demonstrate sporadic occurrence, with only a small number of cases of familial occurrence reported. Diagnosis of PHPV is made through comprehensive eye examination. Nonetheless, final confirmation of the disease is carried out through Magnetic resonance imaging [MRI], Computed tomography [CT] scans and ultrasonography [US] techniques. Differential diagnosis of the disease includes retinoblastoma, which should be ruled out [21].

Congenital Cystic Eye [CCE]

The congenital cystic eye, alternatively known as the Cystic Eyeball, is a rare ocular malformation that arises due to the incapability of optic vesicle to invaginate during the fetal period; this characteristic also makes CCE related to other abnormalities [22]. The cyst is characterized by absence of the anterior and posterior sections of the primary optic vesicle as well as the intraocular structures [22]. Particularly, a remnant of the optic stalk occurs at the intracranial section of one of the optic nerves in the absence of a chiasm, Mainly, these congenital malfunctions affect the brain, cardiovascular system, and the limbs. [23].

Just around the 4th week of gestation, Teratogenesis occurs, which consequently results in the development of a blush, soft and retro-palpebral mass centering the orbit. However, the histological features of this mass differ across individuals [24]. A dense connective tissue surrounds the cyst that resembles the sclera; that attaches the adipose and muscular tissues together. The congenital anomaly has been approximated to occur in the 35th day of gestation. Mainly, such dysgenesis of the vesicles may lead to other complications such as microphthalmia, anophthalmia, or coloboma. Therefore, in rare advanced cases, it leads to the CCE, characterized by the formation of benign tissue filled with fluid [25]. After birth, the cyst persists and replaces the eye within the orbital cavity posteriorly.

Most researches indicate a possibility of inflammation of an eye affected by coloboma. The condition is not hereditary and lacks any secondary prenatal abnormalities. Clearly, the inflammation is severe that the ectodermal elements fail to develop into future eye structures. Additionally, the glial tissues grow rapidly, especially after birth and is mostly unilateral; however, two cases of bilateral CCE have been report [26].

Although there are no confirmed empirical studies that speak of the role of genetic mutations in this disease, yet studies have reported the possible role played by the PAX6 mutations in the CCE. To be specific, the study by Chanas et al [2009] argues that elevated PAX6 expression may result in the demonstration of certain anomalies with the inclusion of the CCE [27]. On the other hand, the involvement of SOX2 and other related genes has been excluded [22].

Congenital cystic eye can be diagnosed through a variety of clinical, histological and radiological features identified through comprehensive examination and laboratory analysis [22]. Radiological examination of the congenital cystic eye usually indicates a large erythematous soft tissue that stretches the upper eyelid and bulges out of the palpebral fissure. A CT scan often reveals a complex mass where the anterior section is irregular and accompanied by soft tissue attenuation. The posterior portion is relatively smooth, unilocular and cystic. The mass lacks any fat or calcification. At the same time, the extraocular muscles and optic nerve are also not visualized [28]. While an MRI conducted on a case of CCE, indicated a complex mass that fills and expands towards the left orbit [23, 24]. One-third of the anterior part was irregular and appeared to be isointense to the muscle. The appearance of the posterior two-thirds was homogenous smooth, pyriform-shaped accompanied by an apex extending towards the optic canal [23, 29].

Importantly, CCE could be effectively managed through healthy living and advanced prenatal care. In particular, the Surveillance Epidemiology technique can be utilized to effectively detect and prevent this disease from occurrence. An administration of effective treatment starts with the early detection during the first trimester of the fetus. The treatment must begin immediately after the birth of the child. Enucleation is the initial procedure followed by the insertion of an ocular transplant and prosthesis [25]. Mainly, during enucleation, the eye is removed leaving the eye muscles and the remaining orbital contents intact [30].

Microphthalmia, Anophthalmia, and Coloboma

Three anomalies comprise the MAC spectrum of ocular malformation; microphthalmia, anophthalmia and coloboma. Microphthalmia, as its names indicates, is the presence of a small eye in the orbit. An eye with an axial length smaller than two standard deviations of the mean for age. In adult eyes, it is typically considered microphthalmia if the axial length is below 21 mm. While anophthalmia is the absence of the eye [31], and coloboma refers to a condition results from the optic fissure failure of closure [32].

The MAC spectrum accounts for an important proportion of blindness in children. The prevalence range of children born with microphthalmia is from 2 to 17 cases per 100,000 births, while anophthalmia cases are 0.6 to 4.2 per 100,000 births, and 2 to 14

per 100,000 are diagnosed with coloboma [33-36].

Although the exact pathogenesis of these mentioned conditions is not fully known, allegedly, common causes include gestational infections such as rubella, herpes simplex virus, and cytomegalovirus [CMV]. Other causes include exposure to X-rays, deficiency of certain vitamins, such as vitamin A, thalidomide exposure, and solvent abuse, mainly through alcoholism [31, 37]. Despite considerable search for credible empirical evidence, no prominent etiological facts could be identified regarding this disease. However, a heterogenous genetic basis characterized by a local disruption in the eye development has been noted [38]. Perhaps the most commendable finding with regards to the genetic role here is a human study that identified mutations in the CHX10 gene as a reason behind this disease, along with the potential role played by mutations in the STRA6, OTX2, or SOX2 gene [39, 40]. Arguably, gene mutation only accounts for minority of cases of microphthalmia. According to Zahrani et al. [2013], colobomatous microphthalmia is associated with delayed development, intractable seizures, abnormalities in the corpus callosum, and the homozygous truncating mutation of C12orf57 [41]. Duplication or mutation of PAX6 genes has also been found to cause these anomalies [42].

Apparently, cases of MAC can be detected during pregnancy. Eyes were observed in early and mid-gestation while microphthalmia was diagnosed in the third trimester of pregnancy or after birth [43, 44]. Examination by ultrasound and magnetic resonance imaging, together with computerized tomography, are normally used for such anomaly's detection both prenatally and after birth. In the case of microphthalmia, the radiological examination involves an ultrasound to show the length of the globe. And radiological CT and MRI scans indicate lack of a globe in the orbit with the presence of soft amorphous tissue in anophthalmia, however, the extraocular muscles would be present [31]. In simple cases of microphthalmia, a normal small globe is seen accompanied by normal signal and density traits of the lens and vitreous that are in a smaller orbit than normal. MRI imaging in cases of colomoba indicates an enlarged prechiasmatic optic nerve. Reduced peripheral enhancement is shown at the lateral section of the optic chiasm [45, 46]. These anomalies are usually present unilaterally, however, rare cases of bilateral form were documented [45, 47, 48].

Dealing with MAC anomalies are mainly a cosmetic issue; however, some people prefer to remove them through surgical incision, an approach that has been regarded risky due to the delicate nature of the eye. Enucleation has also been considered as a viable alternative; however, it causes complications following the spread of anophthalmia to the socket [49]. Mostly, the socket is replaced with silicone, Medpor, or hydroxyapatit. In the case of coloboma, the size and location of the gap caused by coloboma of the eye determines the degree of blindness of the patient, and hence the therapeutically approach [50].

Other Eye-related Abnormal Conditions

Trisomy 13 is a condition that mostly affects the chromosomes during the early stages of fetal development. Normally, the human cells comprise two copies of chromosome 13; however, individuals suffering from trisomy 13 have three copies [51]. Born children with this condition are characterized by intense physical impairment and intellectual disability, and with serious ocular malformations, such as iris coloboma, microphthalmia, and retinal dysplasia [52].

Robert's Syndrome, also known as Appelt-Gerken-Lenz syndrome or Pseudothalidomide syndrome, It is a genetic condition inherited in an autosomal recessive pattern associated with the absence of the limbs and facial impairment [53]. Fetal development, intellectual advancement, and the overall child's growth are considerably slow. The eyes often appear prominent as the result of shallow orbits. Hypertelorism and microphthalmia can be present. The sclerae can have a bluish hue. Cataracts and central corneal clouding plus scleralization and vascularization of the peripheral corneas are sometimes seen. Lid colobomas and down-slanting palpebral fissures may be present [54].

Congenital Rubella Syndrome is a condition manifested in a developing fetus of mothers with a history of rubella. It is associated with sensorineural deafness, microphthalmia, retinopathy, and cataract. Intellectual impairment and organ failures are experienced after birth [55].

MATERIAL AND METHODS:

After an extensive review in the literature to better understand posterior ocular anomalies, a retrospective chart review of all patients diagnosed with posterior ophthalmic malformations at King Abdulaziz University Hospital [KAUH] and King Khaled Eye Specialist Hospital [KKESH] from the year 2000 until 2018. The data collected were demographic information, age at diagnosis, medical history, laterality, and the cause of posterior ophthalmic malformation with histology finding.

Descriptive statistics such as percentage, mean and standard deviation will be used for demographic data and disease characteristics.

RESULTS:

Only cases with tissue diagnosis were extracted from

the histopathology database. These cases presented to KKESH and KAUH from the year 1990 to 2018. Total of seven out of twelve histopathologically confirmed cases of posterior ophthalmic malformation were included in this study.

Out of these, 85.7% were females compared to 14.3% males. The right eye was involved in 57.1 % of cases compared to 42.9% of left eye involvement with no cases of bilateral involvement. Out of the reported cases, 85.7% [6/7] were Saudis compared to 14.3% [1/7] Non-Saudis. The Saudi patients were distributed as follows: 66.6% [4/6] of cases were from the central region, 16.6% [1/6] from the Eastern region and 16.6% [1/6]from the Southern region. There were no reported cases from northern or western regions. History of consanguinity with the parents being first degree relatives was documented in 1 case only. which were suffering from hearing problem.

Systemic illness during pregnancy was documented in 14.3% of the mothers. 85.7% were product of full term with history of NICU incubator admission in 28.5%. All cases were products of normal spontaneous vaginal delivery. The milestones were up to age in 85.7 % of cases.

The reported data shows positive systemic anomaly in 28.6% [2/7] of cases with delayed milestones in the form of generalized hypotony [1/2] and hearing problem [1/2]. No cases had history of any intervention before presentation to KKESH or KAUH.

In terms of management, evisceration was performed for the microphthalmic eye in 71.4%, while enucleation was performed in 28.6%. Criteria for the procedure choice was not documented.

All reported cases showed abnormal corneas in the form of abnormal irregular epithelium and thickened bowman's layer in 42.9%, scarred or irregular Bowman's layer in 28.6% of cases and calcification in 14.3% indicating associated Band keratopathy. 71.4% of cases had abnormal corneal stromal lamellar architecture and abnormal thickened Descemet's membrane while the endothelium was abnormal in 57.1 % of cases due to either Descemet's membrane detachment or iridocorneal adhesions with or without ciliary body involvement, representing some form of anterior segment dysgenesis.

71.4% of the microphthalmic eyes have shown anterior chamber [AC] angle dysgenesis, where the anterior chamber was very shallow in [5/7] and the angle structures were unidentifiable in one case.

Lens was present and opaque in 57.1% with microspherophakia in 25% [1/4], while the lens was absent in 42.9% of cases. Lens coloboma was not identified in any of the cases.

The choroid was found to be either abnormally scarred or atrophic in almost all cases while normal in one of the cases.

RPE was either thickened or dysplastic in 42.9%, atrophic in 14.3% and normal in 14.3 %.

Retina was abnormally gliotic in 71.4% [5/7], dysplastic in 42.9% [3/7], atrophic in 28.6 % [2/7] and hyperplastic in 1 case.

DISCUSSION:

The current study aimed to start national data base speculating pathological and genetics for all cases of posterior ophthalmic malformation as both hospitals are major referral centres for eye and genetic diseases in the country.

Indeed, despite the discovery of many genes that cause eye malformation still most of cases are genetically undiagnosed and needs investigation and correlation to the pathology spectrum with special advantage and promising result in our highly consanguineous community.

Eye development is highly delicate and complex and requires normal developmental environment and coordination with multiple genetic pathways directly or indirectly. Early embryology includes major events [optic vesicle formation, optic cup formation, optic fissure closure] and controlled by important genetic pathways [7].

While the eye grows during infancy it becomes more tolerant to mutations and damages subsequently, the less sever minor eye malformation presented later in infancy [56].

Unilaterality predominance of eye malformation suggest that ocular causes and genes mutations are responsible more about organizing the growth and function of the eye rather than systemic [57]. These genes are more sensitive and pliable to mutations and highly expressive this support why minor eye malformations are more common than major types, however we assume that more severe major eye or systemic mutation are masked by stillbirth or miscarriages despite this was not significant in the current findings and need to be investigated later in second steps.

Anterior segment dysgenics was more commonly associated with posterior malformations and this fact was supported with many previous studies [58, 59]. Normal intraocular pressure plays a crucial role in determining the total axial length and corneal size during infancy, in our data this supported by dysgentic anterior chamber angle and abnormal corneal presentation in most of the cases. Sox2 and Pax6 are highly expressed during lens induction and responsible for maintaining eye growth and mutation analysis should be considered as first line.

The basis of microphthalmia is severely stunting ocular condition which histopathological exam shows retinal dysplastic and gliotic. The significance of the

clinical features has been identified only in minority of cases and was associated with first degree family consanguinity in one case which was suffering from hearing problems and similar presentation were reported with SOX2 association in the literatures [60].

Other systemic finding was generalized hypotony and this similar presentation was studied with known gene mutation in the Saudi population, this gene is SLC18A2 [61]. However, our patient was not suffering from any other global developmental delay.

CONCLUSION:

Some posterior ophthalmic malformations are rare, however, they come with great impact on families and a challenge for ophthalmologists, in this sense, a thorough examination and prenatal care and attention are required for best management. This work summarizes the cause, presentation and treatment of the most common pathologies, with a case series of patients diagnosed with such malformation through histopathological analysis.

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