Case Report

Windows to the Soul- Heterochromia Iridis

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ABSTRACT

Eye colour in humans is a distinct character, and an important trait of an individual's personality. Heterochromia iridis is a unique phenotype. It is an exceedingly rare condition caused by mutations in genes responsible for synthesis, distribution, and concentration of the melanin pigment in the irises of the eye. Many health disorders and syndromes are associated with heterochromia. Here, we report for the first time in Pakistan, two unique individuals with sectoral heterochromia. This report also addresses the social and psychological pressures these remarkable individuals face in the Pakistani society.

Keywords: Sectoral heterochromia, Waardenburg syndrome, social pressure, Consanguinity, Pakistan.

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INTRODUCTION

Eye colour in humans shows a broad spectrum ranging from lightest shades of blue to darkest shades of brown. The presence of melanin pigment in the iris determines the colour pattern. Heterochromia iridis (heterochromia – variance in colour, iridium – within the iris of one eye) is described as an ocular condition in which the colour of the irises of the eyes deviate from each other. It is a rare condition and has an occurrence of 1 in every 200,000 individuals in the U.S. Heterochromia in the iris can be either complete, partial/ sectoral, or acquired (Imesch et al., 1997). It may arise either due to lack of pigment (Hypopigmentation) or an excess of pigment (Hyperpigmentation) in one iris as compared to the other (Oluwole et al., 2011).

In complete heterochromia, the colour of both irises entirely differs from each other, whereas in the case of partial/ sectoral heterochromia, which is exceedingly rare, in which only a portion of the iris shows a different colour. Acquired heterochromia may occur due to injury, inflammation, the use of certain eye drops that damages the iris (Imesch et al., 1997).Also, there is another subtype referred to as central heterochromia, in which the center portion of both irises consists of different colours.

Patients exhibiting heterochromia generally do not demonstrate any visual complaints, however, heterochromia is occasionally linked with rare congenital diseases and syndromes like Waardenburg Syndrome, Sturge–Weber syndrome, Horner's syndrome, Hirschsprung's disease, Parry–Romberg syndrome, and Fuchs heterochromia iridocyclitis (Rennie et al., 2012) (Table 1). Apart from the heterochromatic irises associated with Waardenburg Syndrome, homochromatic irises have also been reported in previous studies (Nusrat et al., 2018; Oluwole et al., 2011).

Sectoral heterochromia is an extremely rare condition. The is no literature evidence indicating the presence of sectoral heterochromia in Pakistan and the stigmas associated with the affected individuals. Henceforth, this report represents the incidence of this condition and the outcomes associated with it in the Pakistani population.

Disorders	Indications	References
Hirschsprung's disease	Constipation, Vomiting, Abdominal pain	(Cui et al., 2013)
Congenital Horner's syndrome	Miosis, Anisocoria, Ptosis, Delayed dilation of pupil	(Ulusoy et al., 2016)
Waardenburg Syndrome	Sensorineural hearing loss, Pigment abnormalities, White forelock of hair	(Shelby, 2017)
Sturge–Weber syndrome	Port-wine birthmark, Skin abnormalities	(Higueros et al., 2017)
Fuchs heterochromia iridocyclitis	Low grade asymptomatic uveitis, Visual deterioration	(Pillai, 2017)
Parry–Romberg syndrome	Progressive deterioration of the skin and soft tissues of half the face	(Schultz et al., 2019)

Table 1: Conditions Associated with Heterochromia

Case Description

Case 1- A male child, aged about 7 years is having light silver shaded, Blue-coloured left iris and light silver shaded Blue, and Brown coloured right iris (Figure 1- A). This is a case of sectoral heterochromia iridis. The child was born with sectoral heterochromia and was observed by the parents soon after the child's birth. Ocular examination revealed no decreased visual acuity. Apart from heterochromia, the child is suffering from sensorineural hearing loss and lacks speaking capability, which indicates the presence of Waardenburg syndrome (Type 2). There is an absence of depigmentation in any part of his hair or skin. There is no inflammation nor any tumour present in his eye. The parents of the child are first cousins and belong to the Niazi caste. Parents and siblings of the affected child did not show the presence of heterochromia and have brown-coloured eyes. There has been no report of different coloured eyes in any family member for the past four generations. The boy is healthy and in good physical condition.

Case 2- A male child, aged about 6 years is having bright, Blue-coloured left iris and bright blue and dark brown coloured left iris (Figure 1- B). Sectoral heterochromia iridis is present in the child. Sectoral heterochromia was observed by the parents of the child after birth. The child is not suffering from hearing loss, nor any other

abnormality associated with heterochromia. The child also did not show any signs of declined visual acuity. Depigmentation of the hair and skin was also absent in the child. The parents of the child are first cousins and belong to Kundi caste. Neither siblings nor the parents of the child have heterochromia and have brown-coloured eyes. No other family member has been reported with heterochromia or blue-coloured eyes for the past four generations. The child has not suffered from any major disease since birth and has good health condition. Both affected individuals suffered from social and physiological pressure due to their rare condition. This is due to the lack of public awareness associated with the condition. The parents were offered the option of cosmetic lenses for their affected children.

Individuals		**Case 1**	**Case 2**
Age (years)		7	6
Gender		Male	Male
Hair colour		Black	Black
Skin colour		Normal	Normal
Visual acuity	**RE**	6/60	6/60
	LE	6/60	6/60
Iris colour	**RE**	Light Blue and Brown	Dark Blue and Brown
	LE	Light Blue	Dark Blue
Photophobia		No	No
Colour blindness		No	No
Nystagmus		No	No
Fundus		Normal	Normal
Heterochromia		Present	Present
Age of onset		Congenital	Congenital

Table 2: Details of clinical features in affected cases with Heterochromia

DISCUSSIONS

Eye colour is a distinctive feature in humans and varies from person to person. There are four major factors which influence iris pigmentation: the concentration of pigment in the iris melanocytes, the pigment granules within the pigment epithelium, the nature of melanin pigment within the iris

melanocytes and the absorption and light-scattering properties of the extracellular stromal matrix (Imesch et al., 1997). The quantity of melanin pigment in the iris mainly determines eye colour. Higher melanin concentration leads to brown colour whereas, diminished melanin shows blue colour in eyes. Eye colour was thought to be inherited as a simple mendelian trait, in which brown-colour was considered dominant and blue-colour as a recessive trait, but recent studies suggest that eye colour may follow polygenic mode of inheritance (Sturm & Frudakis et al., 2004). A total of 15 genes have been linked with eye colour. Two major genes *OCA2* and *HERC2* are widely associated with iris colour. Single-nucleotide polymorphisms (SNPs) in *OCA2* could be the cause of a variety of eye colour in humans (Duffy et al., 2007). Heterochromia is a condition that can be classified, as either acquired, congenital or genetic. Very rarely it is linked with any underlying disease or syndrome. The 8-HTP pathway is responsible for the production of melanin pigment. Mutations in the genes caused by chromosomal homogeneity corresponding to the 8-HTP pathway may lead to the development of heterochromia iridis (Rennie et al., 2012). The affected cases presented in this study were visited, and a detailed clinical examination was performed by a local ophthalmologist. Both patients showed no nystagmus, and visual acuity measuring 6/60 Snellen in both eyes. Fundus examination in both individuals revealed no significant pathology with normal retinal vessels and fundus pigmentation. Colour vision testing and light sensitivity testing were performed for affected individuals. Any other incidence of systemic or other ocular anomalies along with mental retardation, night blindness, and photophobia were not observed in any of the affected individuals. A brief rundown of clinical evaluation is presented in Table 2.

In the presented cases, one out of two affected individuals with heterochromia showed additional symptoms indicating the presence of Waardenburg syndrome. There are four subtypes of Waardenburg syndrome (Type I-IV), type I and III show a dominant inheritance pattern, whereas type II and IV show recessive pattern (Read & Newton et al., 1997). Mutations in the *EDN3, EDNRB, MITF, PAX3, SNAI2*, and *SOX10* genes have been found to be implicated with Waardenburg syndrome. These genes are involved in the formation and development of several types of cells, including pigment-producing cells called

melanocytes (Nusrat et al., 2018). SNPs in any of these genes result in the abnormal development of melanocytes, leading to irregular pigmentation of the eye, hair, and skin (Sturm et al., 2009).

A unique colour pattern has been observed in both the affected children, that has not been previously reported in the literature. Both affected individuals suffered from social and psychological pressure due to their unique condition. Keeping in mind the superstitious beliefs imbedded in the Pakistani population, there is little awareness with regards to heterochromia, which is regarded as more of a disorder rather than a unique condition. Molecular genetic analysis of the affected individuals will be carried out to check for any novel or previously known mutations in targeted genes.

CONCLUSION

Heterochromia is a unique phenotype very rarely reported in the Pakistani population. Due to the lack of awareness about this condition, there is an enigma among the population whereas the affected individuals are stigmatized and face social and physiological pressures. It is very important to report such exceptional cases, to raise public consciousness about such patients, and to provide better support and design management strategies. Since many disorders are associated with Heterochromia, patients must undergo a detailed medical examination to uncover any underlying condition or disorder.

Compliance with Ethical Standards

Conflict of Interest None

Funding This research did not receive any specific grant from funding agencies.

Declaration of Consent This study was approved by the Ethics Review Committee of International Islamic University, Islamabad, Pakistan. Informed written consent was taken from the parents to publish their respective child's rare condition with pictorial references.

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Figure 1: Sectoral heterochromia in affected male children (A) Case 1 (B) Case 2

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