

Waardenburg Syndrome Type 1

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Key words: Auditory-pigmentary syndrome, dystopia canthorum, Heterochromia iridium, Waardenburg syndrome

Auditory-pigmentary syndromes are caused by the physical absence of melanocytes from the skin, hair, eyes, or stria vascularis of the cochlea. Dominantly inherited examples with patchy depigmentation are usually labeled Waardenburg syndrome (WS). Type I WS, characterized by dystopia canthorum, is caused by loss of function mutations in the *PAX3* gene. Type II WS is a heterogeneous group, about 15% of whom are heterozygous for mutations in the microphthalmia associate transcription factor (*MITF*) gene. Type III WS (Klein-Waardenburg syndrome, with abnormalities of the arms) is an extreme presentation of type I; some but not all patients are homozygous. Type IV

WS (Shah-Waardenburg syndrome with Hirschsprung disease) can be caused by mutations in the genes for endothelin-3 or one of its receptors, endothelin receptor B (EDNRB). All these forms show marked variability even within families, and it is not possible to predict the severity, even when a mutation is detected.^[1] We hereby report a case of Waardenburg syndrome type 1.

A 12-year-old female presented with her mother complaining of a difference in the color of her eyes along with deafness and mutism since birth. Ocular examination (OU) revealed uncorrected visual acuity of 6/6 on Snellen's Chart with heterochromia iridium. Fundus were within normal limits with no pigmentary changes. There was dystopia canthorum with an intercanthal distance of 42 mm, an interpupillary distance of 58 mm, a flat nasal bridge, and an upslanting palpebral fissure [Fig. 1]. W index was found to be 2.43, indicating dystopia canthorum [Fig. 2]. Family history revealed no history of consanguinity and similar abnormality in any sibling or parent. The patient had sensorineural deafness on pure-tone audiometry. A probable diagnosis of Type 1 WS was made based on history, clinical assessment, and pure-tone audiometry.

The patient was counseled regarding the condition, social and vocational training, and rehabilitation of the patient.

Discussion

Auditory-pigmentary syndromes are caused by the physical absence of melanocytes from the skin, hair, eyes, or stria

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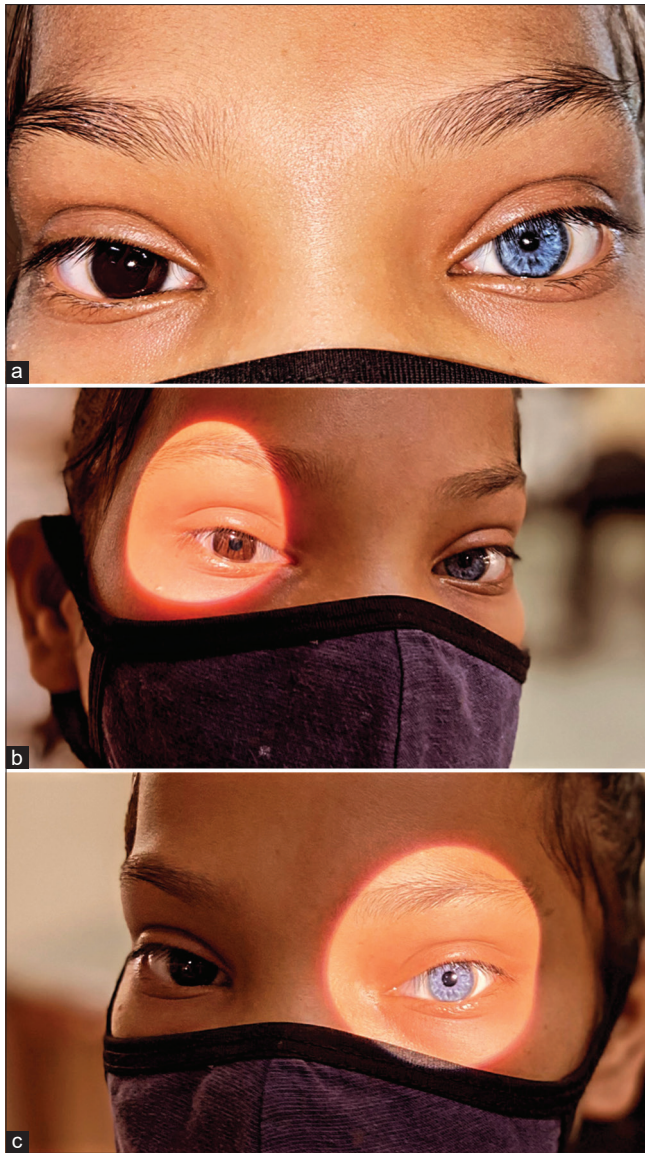


Figure 1: The figure shows a clinical image depicting clinical features of Waardenburg syndrome type 1; (Dystopia canthorum, flat nasal root and Heterochromia Iridium).

vascularis of the cochlea. Dominantly inherited examples with patchy depigmentation are usually labeled WS. A diagnosis of WS needs two major, or one major and two minor criteria of the following [Table 1].

In our patient, congenital SNHL, heterochromia iridium, dystopia canthorum, and broad and high nasal root were present. Dystopia canthorum is the most penetrant feature of WS 1, being present in 99% of those affected. Dystopia presents with the appearance of fusion of inner eyelids medially leading to a reduction in the medial sclerae. Dystopia canthorum shows variable expressivity/degree in these patients; thus, W index is measured to firmly diagnose dystopia canthorum.

Arias *et al.*^[3] reported that both dystopia canthorum and blepharophimosis show variable expressivity, which may be confused with a non-penetrance of this sign; to diagnose it

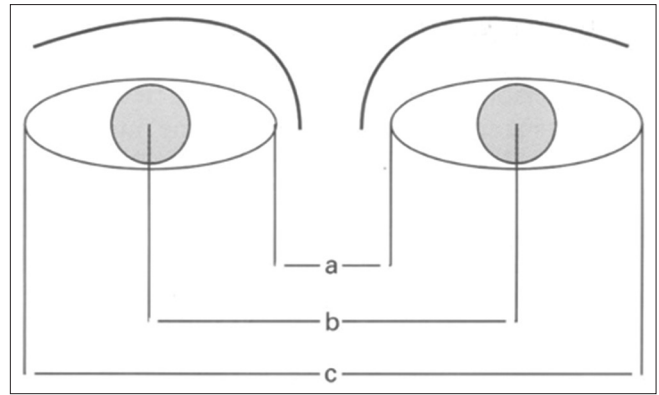


Figure 2: To calculate the W index: (1) Measure (a-c) in mm using a rigid ruler held against the face. (2) Calculate $X = (2a - 0.2119c - 3.909)/c$. (3) Calculate $Y = (2a - 0.2479b - 3.909)/b$. (4) Calculate $W = X + Y + a/b$. WS type I is diagnosed if the average W of all affected family members is 1.95 or more. (a-c) is measured using a rigid ruler.

Table 1: Diagnostic criteria of WS

Major criteria	Minor criteria
Congenital sensorineural hearing loss	Congenital leukoderma:
Pigmentary disturbances of iris	several areas of hypopigmented skin
(a) Complete heterochromia iridium: two eyes of different color	Synophrys or medial eyebrow flare
(b) Partial or segmental heterochromia: segments of blue or brown pigmentation in one or both eyes	Broad and high nasal root
(c) Hypoplastic blue eyes: characteristic brilliant blue in both eyes	Hypoplasia of alae nasi
Hair hypopigmentation: white forelock	Premature graying of hair: scalp hair, predominantly, white before age 30
Dystopia canthorum; W index >1.95	
Affect first-degree relative	

firmly, W index differentiated dystopic from the non-dystopic subject. W index >1.75 indicates a true dystopic patient. W index in our patient was 2.43.

Iris heterochromia may be complete or partial. In complete heterochromia iridium, each iris is of a different color, whereas in partial heterochromia iridium, the differently colored area of the iris is sharply demarcated from the remainder. Astakhov *et al.*^[4] reported a case of complete bilateral iris heterochromia and impaired choroidal pigmentation, but the structural and functional properties of the retina and choroid were preserved. Liu *et al.*^[5] reported that sensorineural hearing loss (77%) and heterochromia iridium (47%) were the two most important diagnostic indicators for WS 2; both were more common in type 2 than in type 1, and both of these signs were present in our patient. Broad and high nasal root, hypertrichosis, and hypoplasia of the alae nasi are other features associated with dystopia canthorum in WS 1.

Heterochromia Iridium in any patient must be dealt with caution and a complete checkup including ENT and dermatological examination should be performed to rule out auditory-pigmentary syndromes. Inheritance of WS is autosomal-dominant, and *de novo* cases of this rare syndrome are mentioned in the medical literature; thus, genetic counseling plays a great role. Early diagnosis of WS from heterochromia

iridium may aid in the initiation of social and vocational training and rehabilitation of these patients.

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Conflicts of interest

There are no conflicts of interest.

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