

Waardenburg Syndrome Type 1 Coexisting with Unilateral Glaucoma: A Case Report

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Abstract: Waardenburg syndrome (WS) is a rare disorder of neural crest cell development classified into four main clinical and genetic phenotypes. The range and severity of associated symptoms and findings may vary greatly from case to case. There are few reports of WS associated with ocular disorders. Here, we describe a case of WS type1 combined with open-angle glaucoma and emphasize the importance of observation of comorbidities that can coexist with the syndrome. Early diagnosis and intervention can lead to better outcomes.

Keywords: Waardenburg Syndrome; Ocular Manifestations; Glaucoma; Genetic Counseling; Case report.

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1. Introduction

Waardenburg syndrome (WS) is a rare genetically clinical entity with a variety of manifestations that can produce sensorineural hearing loss, pigmentary disturbances of the skin, hair and eye, and defects of neural crest derived tissues firstly published by the ophthalmologist from the Netherlands Petrus Johannes Waardenburg in the American Journal of Human Genetics in 1951. The incidence of the syndrome is approximately 1:42,000 births worldwide, with no preference for race or gender [1].

It accounts for more than 2% of all congenital hearing loss, which is the most common clinical feature of WS. This syndrome is classified into four types according to characteristics and additional signs, as WS1, WS2, WS3, and WS4 [2]. Diagnostic criteria for WS1 have been proposed by the Waardenburg Consortium in 1992 [3], with five major and five minor diagnostic criteria (Table 1). Association of at least 2 major, or 1 major and at least 2 minor clinical criteria are necessary for the diagnosis of WS.

Table 1. Diagnostic criteria for Waardenburg Syndrome type 1^a.

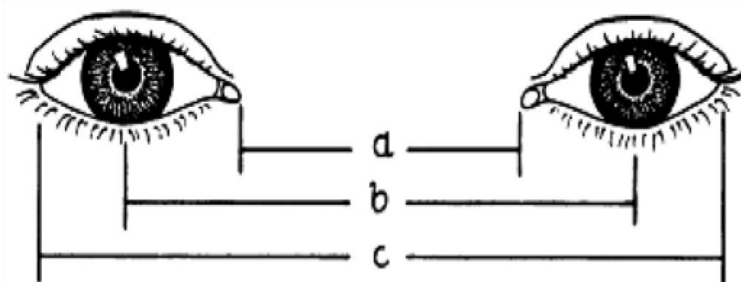
Major Criteria	Minor Criteria
Distopia canthorum; W index >1,95 (Figure 1)	1. Congenital leukoderma
Pigmentary disturbances of iris	2. Synophrys or medial eyebrow flare
Hair hypopigmentation	3. Broad high nasal root
Congenital sensorineural hearing loss	4. Premature gray hair (<30 years)
Affected first-degree relative	5. Hypoplasia of alae nasi

^a Criteria proposed by the Waardenburg Consortium [3].

Dystopia canthorum is the most frequent ophthalmological feature of WS1 followed by hypopigmentation of the iris and retina. WS2 is characterized by congenital sensorineural hearing loss, pigmentary disturbances of the iris and hair hypopigmentation but lacks dystopia canthorum. WS3 is similar to WS1 but it is associated with musculoskeletal abnormalities. WS4 is associated with features of Hirschsprung disease and is also called Shah-WS [2,3]. Most cases of WS 1 and WS2 are inherited as autosomal dominant, WS3 could be sporadic or autosomal dominant, and WS4 is inherited as autosomal recessive [4].

Dystopia canthorum refers to increased distance between the medial corners of the eyelids (inner canthi), while the interpupillary distance is normal and is identified by calculation of the Waardenburg index (W index) (Figure 1), based on the distance between the inner canthi, pupils, and the outer canthi. A W index > 1.95 in Caucasian [3], and >2.10 in Chinese shows dystopia [5]. The highly variable clinical manifestations of WS due to variations in the expressivity of affected genes, even within a single family, make it difficult to reach a definitive diagnosis.

Figure 1. Ocular measurements necessary to calculate W index (in millimeters). Inner canthal distance (A), interpupillary distance (B), and outer canthal distance (C). A result showing a W index of more than 1.95 is consistent with a diagnosis of dystopia canthorum.



$$X = [2a - (0.2119c - 3.909)]/c.$$

$$Y = [2a - (0.2479b + 3.909)]/b.$$

$$W \text{ index} = X + Y + a/b$$

Glaucoma is a group of diseases characterized as a degenerative optic neuropathy with cupping of the optic nerve head that is a leading cause of blindness worldwide [6]. Primary Open Angle Glaucoma is an often-unrecognized disease due to its slow course and lack of symptoms. Due to its potential to cause permanent vision loss, it is important to understand how systemic conditions can be associated with or increase the risk for developing this condition.

Studies reporting ocular manifestations of WS are few, mostly focusing on the abnormalities of the iris. Rare reports have described details of fundus findings or glaucoma [7-10]. Herein, we want to describe a case of WS1 combined with open-angle glaucoma and emphasize the importance of a detailed observation of comorbidities that can coexist with the syndrome.

2. Case Report

A 41-year-old male presented to our service for a routine ophthalmologic examination. Physical examination revealed hypertrichosis of the medial part of the eyebrows (synophrys) and dystopia canthorum; the W index was found to be 1.97. Hypopigmentation of the skin or hair was not found. In ophthalmic examination, the patient was emmetropic and had 1.0 vision in both eyes (OU). Eye movements were free in all directions. There was total heterochromia iridum. The right iris was brown, and the left iris was blue

(Figure 2). The pupils were round and equal in size. Intraocular pressure (IOP) was 18 mmHg in right eye (RE) and 25 mmHg in left eye (LE).

Figure 2. Iris Heterochromia with left eye hypochromia, dystopia canthorum, and siphrys.



Gonioscopy showed open angles with broad ciliary body band OU. The right ocular fundus was darker in color than the left, and an excavated optic nerve head was found in the left (Figure 3). Optical Coherence Tomography (OCT) showed diffuse loss of the retinal nerve fiber layer (RNFL) in LE. The central corneal thickness of the patient was 504 μm in RE and 499 μm in LE. He started on topical latanoprost 0.005% once daily, and on follow up after one month, his IOP was normal. Audiometry showed bilateral sensorineural hearing loss, more severe in the left (Figure 4).

Figure 3. A. Fundus image showing normal fundus in the right eye, B. showing salmon and hypopigmented fundus due to a lack of pigmentation in the retinal pigment epithelium (RPE) layer (white arrow), and an excavated optic nerve head glaucomatous. Black arrows indicate the extent of cupping in the optic nerve head.

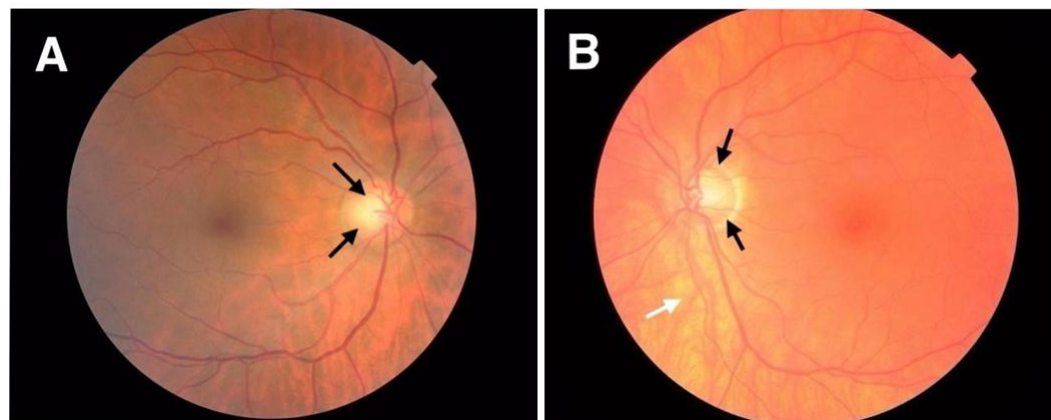
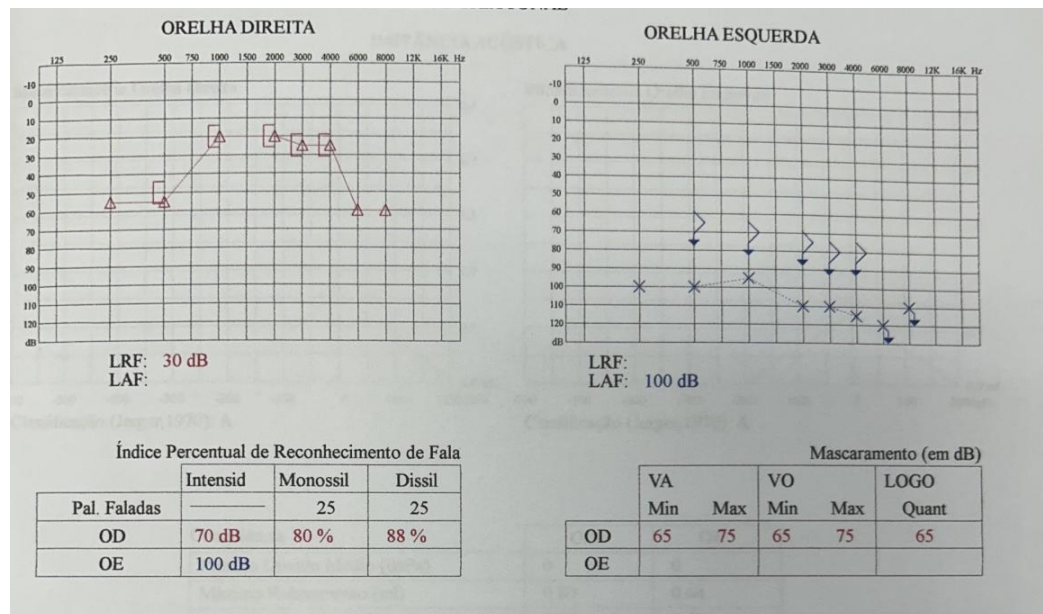


Figure 4. Audiometry showing sensorineural hearing loss at 250Hz, 500Hz, 6KHz and 8KHz on the right, and profound hearing loss on the left.



There was no history of any ocular trauma or any topical or systemic drug use, malformation of upper extremities or Hirschsprung disease. A probable diagnosis of WS1 was made based on history, clinical features, and audiometry. Unfortunately, the patient and their parents did not undergo genetic testing. According to the patient he has six sibs, one of whom had heterochromia and hearing loss.

3. Discussion

Characteristic phenotypic features of WS can be recognized immediately or soon after birth. Genetic testing for confirmation of diagnosis is available [9], however, diagnosis of WS can be made clinically, according to the Waardenburg Consortium criteria [3]. The syndrome is caused by mutations of several genes including paired box gene (PAX3), microphthalmia-associated transcription factor (MITF), KIT ligand (KITLG), snail homolog 2 (SNAI2), endothelin 3 (EDN3), endothelin receptor type B (ENDRB) and sex determining region y-box-10 (SOX10) [11]. Mutation in PAX3 gene is mainly responsible for the clinical features of WS1 and WS3, whereas mutation in genes MITF, KITLG, SOX 10 and SNAI2 are identified in WS2. Genetic mutations in EDN3 and EDNRB have been implicated in WS4.

Although not currently fully understood, all these genes are involved in the division and migration of neural crest cells during embryonic development, including melanocytes of the skin and inner ear, glia, and neurons of the peripheral and enteric nervous systems, and some of the craniofacial skeletal tissue [2]. In WS 1, PAX3 is the most pathogenic gene, resulting in abnormal development in the neural crest during early development. Up to date, dozens of mutations in PAX3 have been identified, including missense mutations, frameshift mutations, and insertions/deletions. According to WS1 diagnostic criteria [3], there are four features of major criteria (neural hearing loss, dystopia canthorum, abnormal pigmentation of the iris, affected first-degree relative), and one minor criteria (synophrys) in this case.

Iris heterochromia is found in 47% of individuals with WS and may be complete or partial. In complete heterochromia, each iris is of a different color, whereas in partial heterochromia differently colored area of the iris is usually a radial segment. Bilateral cases may be symmetrical or asymmetrical. Our patient had complete heterochromia. Hearing loss (77%) has a sensorineural character, and is usually non-progressive, varying from

slight to profound. WS1 individuals were found to be more common, more severe and more likely to feature the bilateral form. In contrast to late identifying of hearing loss, heterochromia iridum may imply an early diagnosis of WS [12]. The medial eyebrow flare or synophrys is seen in our case. This feature is usually found in 63-73% of WS patients.

Despite the pattern of fundus pigmentation not considered diagnostic criteria for WS [12], fundus pigmentary abnormalities were found in approximately one-third of patients with WS [13]. Müllner-Eidenböck et al. [14] consider alteration in fundus pigmentation to be an integral part of this syndrome, with ipsilateral connections between the iris and fundus. Abnormalities of the iris in WS have been documented on electron microscopy to represent fewer melanocytes in the hypopigmented blue region compared with the normal brown region, and a substantial reduction in the melanosome size in the blue region is believed to be related to a defect in neural crest cell migration and melanin production. Abnormal ocular findings are diverse in WS. Patients with hypopigmentation of retinal pigment epithelium without macular hypoplasia may not be related to reduced visual acuity in WS [15], as observed in our case.

Ocular manifestations, such strabismus, telecanthus, cataract, glaucoma, maculopathy, and branch retinal vein occlusion have been described previously and may be the first signs detected [7-16]. These eyes must be examined carefully and, if necessary, treated promptly to minimize any risk of complications. The management is often challenging and requires a multidisciplinary approach according to the involvement of different systems and the severity of disease.

Previous cases have been described linking WS with increased risk of glaucoma [7-9]. Few studies have reported unilateral glaucoma in patients with WS1 [17-19] while Nork et al [20] and Gupta and Aggarwal [7] reported cases of WS with bilateral glaucoma presenting with narrow and open irido-corneal angles, respectively. Abdelrahman and Amin [8] described a case of WS associated with juvenile open angle juvenile glaucoma in a 20-year-old Egyptian man. This association should be investigated with a larger number of WS cases. A possible mechanism could be that both ocular melanocytes and iridocorneal angle structures, such as ciliary body and trabecular meshwork are derived from neural crest cells. A defect in pigmentation may therefore lead to developmental abnormalities in these structures. Although developmental disorders of the anterior segment of the eye could be influenced by the neural crest, neither pigmentary dispersion nor angular developmental malformation, as seen in Axenfeld-Rieger syndrome, was observed in this patient. The contribution of the main cranial neural crest to ocular development includes the periocular mesenchyme, which contributes to the formation of the ciliary body and iris stroma, as well as the trabecular meshwork.

Our patient had high intraocular pressure, an enlarged cup- to-disc ratio, and decreased RNFL on OCT attributed to glaucoma. He was treated with anti-glaucoma eye drops and follow-up observation was needed regularly. This finding suggested that not only external abnormalities, but a detailed ophthalmological examination should be performed, and glaucoma should be investigated, to avoid any delay in diagnosis and treatment for patients with WS.

4. Conclusion

WS shows a remarkable diversity in clinical presentation. Although glaucoma has not been considered as an associated characteristic of this syndrome, the neural crest from which iridocorneal angle structures originates may play a role in the pathogenesis of WS. Detecting and treating this medical condition early can lead to a better quality of life for the affected people. Therefore, we emphasize the importance of the complete ophthalmological examination in patients with iris heterochromia, observing mainly the pattern of the fundus pigmentation, optic nerve e intraocular IOP. Once genetic counseling is recommended to discuss recurrence risks, the lack of genetic testing due to patient preference is a limitation of the present report.

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Research Ethics Committee Approval: We declare that the patient approved participation in the study by signing an informed consent form, and that the study followed the ethical guidelines established by the Declaration of Helsinki.

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Conflicts of Interest: All other authors declare no conflicts of interest.

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