Bilateral symmetrical maculopathy and heterochromia in Waardenburg syndrome

Maculopatia simétrica bilateral e heterocromia na síndrome de Waardenburg

Paulo de Tarso Ponte Pierre-Filho[1], **Lucas Linhares Pierre**[1]

[1] Pierre Oftalmologia, Sobral, CE, Brazil.

How to cite:
Pierre-Filho PT, Pierre LL. Bilateral symmetrical maculopathy and heterochromia in Waardenburg syndrome. Rev Bras Oftalmol. 2023;82;e0052.

doi:
https://doi.org/10.37039/1982.8551.20230052

Keywords:
Waardenburg syndrome; Pigmentation disorders; Hearing loss, sensorineural; Incidence

Descritores:
Síndrome de Waardenburg; Transtornos da pigmentação; Perda auditiva neurosensorial; Incidência

Received on:
Apr 8, 2023

Accepted on:
Aug 4, 2023

Corresponding author:
Paulo de Tarso Ponte Pierre-Filho
Avenida Gerardo Rangel, 803, apto.1.400 – Derby Clube
CEP: 62041-380 – Sobral - CE, Brazil
E-mail: paulopierre@hotmail.com

Institution:
Pierre Oftalmologia, Sobral, CE, Brazil.

Conflict of interest:
no conflict of interest.

Financial support:
no financial support for this work.

ABSTRACT

Waardenburg syndrome is a rare congenital genetic disorder characterized by sensorineural hearing loss and pigmentary abnormalities of the hair, skin, and eyes. Based on the different clinical presentations, it is divided into four subtypes as in WS1 to WS4. This report describes a 15-year-old boy who presented with low vision and bilateral hearing loss. His visual acuity was 20/200 in both eyes. Slit-lamp examination revealed complete iris heterochromia, with one blue iris and one brown iris. Fundus examination showed symmetrical pigmentation of the retina and choroid, with atrophy of the pigment epithelium in the macular region, notably also in the eye with normal iris pigment illustrating the broad spectrum of the iris and fundus pigmentation as part of this syndrome. A carefully clinical and ophthalmological evaluation should be done to differentiate various types of Waardenburg syndrome and other associated auditory-pigmentary syndrome. Early diagnosis in some cases may be crucial for the adequate development of patients affected with this condition.

RESUMO

A síndrome de Waardenburg é uma doença genética congênita rara caracterizada por perda auditiva neurossensorial e anormalidades pigmentares do cabelo, da pele e dos olhos. Com base nas diferentes apresentações clínicas, é dividida em quatro subtipos (WS1 a WS4). Este relato descreve o caso de um menino de 15 anos que apresentava baixa visão e perda auditiva bilateral. Sua acuidade visual era de 20/200 em ambos os olhos. O exame em lâmpada de fenda revelou heterocromia completa da íris, com uma íris azul e uma íris marrom. A fundoscopia mostrou pigmentação simétrica da retina e coroide, com atrofia do epitélio pigmentar na região macular, notadamente também no olho com pigmento de íris normal, ilustrando o amplo espectro de pigmentação de íris e fundo como parte dessa síndrome. Uma avaliação clínica e oftalmológica criteriosa deve ser feita para diferenciar os vários tipos de síndrome de Waardenburg e outras síndromes auditivo-pigmentares associadas. O diagnóstico precoce em alguns casos pode ser crucial para o desenvolvimento adequado dos pacientes acometidos por essa condição.

INTRODUCTION

Waardenburg syndrome (WS) is a rare group of genetic conditions that can produce varying degrees of sensorineural hearing loss, pigmentation anomalies, and defects of neural crest derived tissues described in detail by the ophthalmologist Petrus Johannes Waardenburg in 1951. The incidence of WS is estimated at 1:42,000 births worldwide, or 2 to 5% among patients with congenital deafness, without preference for race or gender.[1] This syndrome is clinically and genetically heterogeneous and is clinically classified into four types according to the presence of variable clinical characteristics and additional signs, as WS1, WS2, WS3, and WS4.[2] Diagnostic criteria for WS1 have been proposed by the Waardenburg Consortium,[3] with five major and five minor diagnostic criteria (Table 1). Two major or one major and two minor criteria are necessary for the diagnosis of WS.

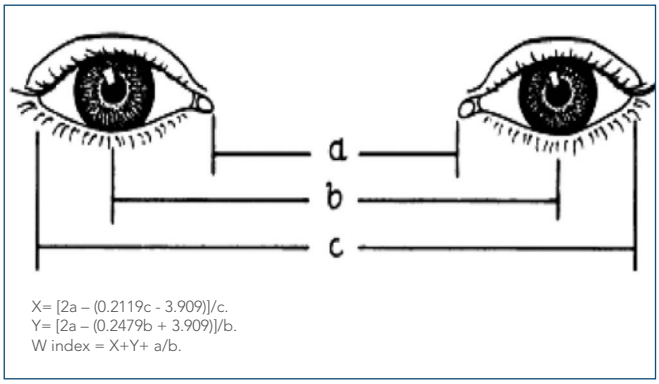
Table 1. Diagnostic criteria for Waadenburg syndrome type 1*

Major criteria	Minor criteria
1. Distopia cantorum; W index >1.95 (Figure 1)	1. Congenital leukoderma
2. Pigmentary disturbances of the iris	2. Synophrys or medial eyebrow flare
3. Hair hypogmentation	3. Broad high nasal root
4. Congenital sensorineural hearing loss	4. Premature gray hair (<30 years)
5. Affect first-degree relative	5.Hypoplasia of alae nasi

Source: Farrer et al.[3]
* Criteria proposed by the Waardenburg Consortium.

WS1 is characterized by dystopia canthorum, congenital sensorineural hearing loss, pigmentary disturbances of the iris and hair hypopigmentation. WS2 lacks dystopia canthorum. WS3 is quite similar to WS1 but it is associated with musculoskeletal abnormalities. WS4 is associated with features of Hirschsprung disease and is also known as Shah-W.[2-4] Dystopia canthorum refers to increased distance between the medial corners of the eyelids (inner canthi), while the interpupillary distance is normal and is determined 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 of more than 1.95 shows dystopia. The highly variable presentations of WS make it difficult to reach a definitive diagnosis. Therefore, genetic testing can be an important method for diagnosing this disease and its subtypes.

Studies reporting ocular manifestations of WS are limited, mostly focusing on the abnormalities of the iris. Rare reports have described details of fundus findings.[5-7] We want to describe here a case of WS and emphasize the importance of a detailed observation of the clinical phenotype and mainly of the pigmentation pattern of the fundus in a patient with bilateral symmetrical retinal pigmentation and complete iris heterochromia.



Source: Farrer et al.[3]

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.

CASE REPORT

A-15-year-old boy was referred to our service with decreased visual acuity in both eyes (OU). Physical examination revealed hypertrichosis of the medial part of the eyebrows (synophrys) and bilateral hearing loss. Hypopigmentation of the skin or hair was not found. In ophthalmic examination, his best corrected visual acuity was 20/200 in OU, and pupils were reactive to light. Cycloplegic refraction were +0,75 -5,00 180º OU. Slit-lamp examination was normal, except for the presence of heterochromia. The right eye (RE) had normal brown iris and the left eye (LE) had a blue iris in the left eye (Figure 2). Intraocular pressure was 17mmHg in RE and 16mmHg in

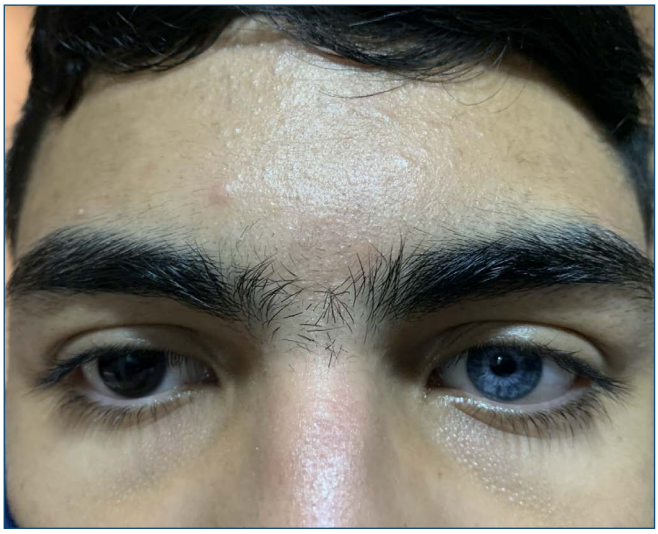


Figure 2. Iris Heterochromia with left eye hypochromia and synophrys.

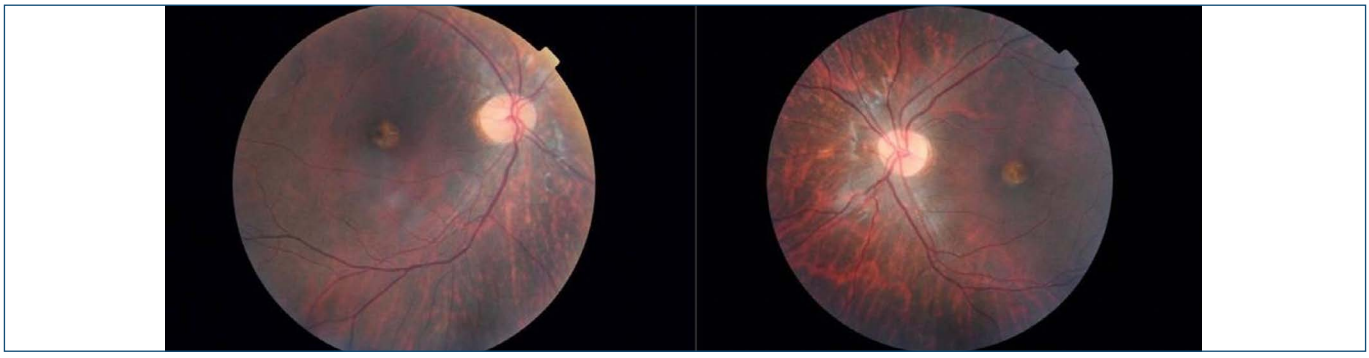


Figure 3. Fundus photo showing symmetric, round, grey-yellowish lesions in the foveal center of each eye.

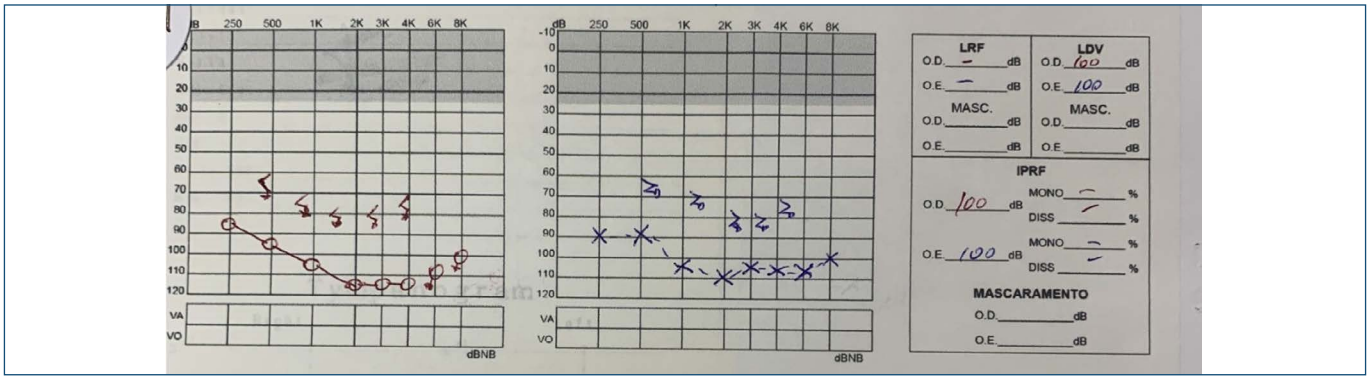


Figure 4. Conventional audiological examination showing profound bilateral sensorineural hearing loss.

LE. Fundus examination showed symmetrical pigmentation of the retina and choroid, with atrophy of the retinal pigment epithelium (RPE) in the macular region, notably also in the eye with normal iris pigment (Figure 3). The W index was found to be 1.71. Conventional audiological examinations showed profound, bilateral, sensorineural hearing loss (Figure 4). 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 WS2 was made based on the history, clinical features, and audiometry. Refractive correction as prescribed and orientation on hearing aids were given. DNA studies were not performed in this patient. He was adopted and his first degree biological family was unavailable for evaluation. Therefore, it is not clear if he presents with an inherited or new mutation.

DISCUSSION

Characteristic morphologic features of WS can be recognized immediately or soon after birth. Genetic testing for confirmation of diagnosis is available; however, diagnosis of WS can be made clinically, according to the Waardenburg Consortium criteria.[3] Most types of WS are autosomal dominant and it has myriad clinical features with incomplete penetrance and highly variable expressivity. Phenotypical features of the WS often vary even among members of one family.[3,4]

The syndrome is caused by mutations of several genes including paired box gene 3 (*PAX3*), microphthalmia-associated transcription factor (*MITF*), snail homolog 2 (*SNAI2*), sex determining region y-box-10 (*SOX10*), endothelin receptor type B (*EDNRB*), and endothelin 3 (*EDN3*), with different frequencies. Variations in any of these genes may result in defective neural crest development and melanocyte differentiation during embryonic development, altering pigmentation of skin, eyes, hair, which can lead to sensorineural hearing impairment.[2]

Sensorineural hearing loss and iris heterochromia are the two most common features of WS2 and both of these signs were present in our patient. Iris heterochromia is found in 47% of individuals with WS and may be complete or partial. Hearing loss (77%) is typically non progressive, either unilateral or bilateral, total or partial. The most common type is bilateral profound loss.[8] Differential diagnosis of WS includes piebalism, Tietz syndrome, oculocutaneous albinism, Vogt-Koyanagy-Harada disease, vitiligo, and other forms of congenital non-progressive sensorineural hearing loss.[8]

The pattern of fundus pigmentation is not considered of diagnostic criteria for WS2;[9] however, fundus

pigmentary abnormalities were found in approximately one-third of patients with WS.[10] Fundus changes are either diffuse hypo pigmentations (albinotic fundus), patchy hypopigmentation or peripheral hypopigmented mottling.

In a study including five Chinese patients with WS1, all patients presented with dystopia canthorum and different colors of the irises and fundi, but none of those showed visible pigmentary changes on their hair and skin. The eye with generalized iris hypopigmentation also had mild retinal hypopigmentation; however, the fundus vessel distribution, macular architectural, and visual acuity were normal.[11]

A case series involving seven patients with WS and intact visual acuity from six families revealed minimal symmetry of the pigmentary abnormality between the two irises with sector hypopigmentation, whereas all bilateral cases of choroidal hypopigmentation showed symmetry. Iris hypopigmentation showed minimal correlation with choroidal hypopigmentation. Optical coherence tomography showed a normal retina, but the subfoveal choroid thickness was decreased in the hypopigmented area of the fundus compared with the opposite normal choroid.[6]

The patient in this study presented with severe bilateral visual impairment and characteristics of complete iris heterochromia and bilateral symmetrical retinal pigmentary disturbances, affecting the macular area. In contrast with our case, Kumawat et al.[12] reported a patient with WS2 that presented bilateral asymmetrical partial heterochromia and suggested that iris and RPE hypochromia may be affected in a corresponding fashion. Also, Müllner-Eidenböck et al.[13] studied Turkish family members with WS 2 who presented with ipsilateral connections between the iris and fundus. However, other recent cases[14] demonstrated diffuse areas of retinal and choroidal hypopigmentation, notably also in the eye with normal iris pigment.[5,14]

Our patient presented with bilateral similar foveal pigmentary changes in spite of dissimilar irises, illustrating the broad spectrum of iris and fundus pigmentation as part of WS. It remains uncertain whether iris heterochromia is associated with retinal alterations in this case, but it highlights the characteristics of the iris and fundus hypochromia, which may provide a clue toward the diagnosis of WS. The association between iris and retinal pigmentation is complex, and unilateral iris heterochromia may be accompanied by bilateral retinal hypopigmentation.[5] Therefore, we cannot conclude whether the relationship between WS and maculopathy was causal or coincidental in this case.

Patients with hypopigmentation of RPE without macular hypoplasia may not be related to reduced visual acuity in WS.[15] This is a rare case of WS2 with bilateral macular pigmentary disturbance causing bilateral visual impairment. We postulated that poor vision is related to the fundus depigmentation; however, amblyopia due to the high refractive error may also not be discarded.

Unfortunately, it was not possible to determine if other members of his biological family were affected by the syndrome, which would help clarify whether the patient had the inherited form of the syndrome or one deriving from spontaneous mutation. Genetic testing and counseling of patients and their parents is advised.

In conclusion, the management of WS can require a multidisciplinary approach according to the involvement of different systems and the severity of disease. It is essential that ophthalmologists recognize patients with WS, as early diagnosis decreases the possibilities of developing complications, as well as regular follow-up is necessary to enable the patient to lead a better quality of life. Moreover, our case also emphasizes the importance of the complete ophthalmological examination in patients with iris heterochromia, observing mainly the pattern of the fundus pigmentation, excluding other issues associated with low visual acuity, which could impair adequate development of affected individuals.

REFERENCES

1. Waadenburg PJ. A new syndrome combining developmental anomalies of the eyelids, eyebrows and nose root with pigmentary defects of the iris and head hair with congenital deafness. Am J Hum Genet, 1951;3(3):195-253.
2. Pingault V, Ente D, Dastot-Le Moal F, Goossens M, Marlin S, et al. Review and update of mutations causing Waardenburg syndrome. Hum Mutat. 2010;31(4):391-406.
3. Farrer LA, Kenneth M. Grundfast, Amos J, Arnos KS, Asher JH Jr, Beighton P, Diehl SR, Fex J, Foy C, Friedman TB, et al. Waardenburg syndrome (WS) type I is caused by defects at multiple 2: first report of the WS consortium. Am J Hum Genet. 1992;50(5):902-13.
4. Read AP, Newton VE. Waadrdenburg syndrome. J Med Genet. 1997;34(8):656-65.
5. Yagnoobi GH, Heidari E. Bilateral symmetric retinal pigmentation versus heterochromia: a case of Waardenburg syndrome. Pak J Ophthalmol. 2013;29(1):50-2.
6. Shields CL, Nickerson SJ, Al-Dahmash S, Shields JA. Waardenburg syndrome: iris and choroidal hypopigmentation: findings on anterior and posterior segment imaging. JAMA Ophthalmol. 2013;131(9):1167-73.
7. Choudhry N, Rao RC. Multimodal ultrawide-field imaging features in waardenburg syndrome. Ophthalmic Surg Lasers Imaging Retina. 2015;46(6):670-3.
8. Chugh JP, Jain P, Chauhan RS, Rathi A. Waardenburg syndrome Tipe II. Delhi J Ophthalmol. 2013;24(1):65-6.
9. Liu XZ, Newton VE, Read AP. Waardenburg syndrome type II: Phenotypic findings and diagnostic criteria. Am J Med Genet. 1995;55(1):95-100.

10. Delleman JW, Hageman MJ. Ophthalmological findings in 34 patients with Waardenburg syndrome. J Pediatr Ophthalmol Strabismus. 1978;15(6):341-5.
11. Wang J, Li S, Xiao X, Wang P, Guo X, Zhang Q, et al. PAX3 mutations and clinical characteristics in Chinese patients with Waardenburg syndrome type 1 Mol Vis. 2010;16:1146-53.
12. Kumawat D, Kumar V, Sahay P, Nongrem G, Chandra P. Bilateral asymmetrical partial heterochromia of iris and fundus in Waardenburg syndrome type 2A with a novel MITF gene mutation. Indian J Ophthalmol. 2019;67(9):1481-3.
13. Müllner-Eidenböck A, Moser E, Frisch H, Read AP. Waardenburg syndrome type 2 in a Turkish family: implications for the importance of the pattern of fundus pigmentation. Br J Ophthalmol. 2001;85(11):1384-6.
14. Park JG, Randhawa S, Capone A Jr. Iris heterochromia and choroidal hypopigmentation in Waardenburg syndrome. Ophthalmology. 2023;130(1):55.
15. Chua SW, Mohd Khialdin, S, Mustapha M, Md Din N, Yong MH. Association of type II Waardenburg syndrome with hypermetropic amblyopia. Int J Ophthalmol. 2022;15(4):677-80.