Juvenile Open-angle Glaucoma With Waardenburg Syndrome: A Case Report

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Abstract: Waardenburg syndrome (WS) is a genetic disorder resulting in anomalies of derivatives of neural crest cells during development. Patients tend to have variable degrees of pigmentary defects affecting skin, hair, and irides in addition to hearing loss and possible systemic neurological associations. Elevation of the intraocular pressure has been reported in several adult patients with WS. We report the first case of WS to be associated with juvenile open-angle glaucoma in a 20-year-old Egyptian man thus expanding the spectrum of the types of glaucoma that can coexist with the syndrome.

Key Words: Waardenburg syndrome, glaucoma, juvenile, neural crest cells, heterochromia

Waardenburg syndrome (WS) is a rare genetic disorder characterized by anomalies in some of the structures developing from the neural crest. Clinical findings of the disease involve different degrees of pigmentary defects of the hair, skin, and irides in addition to sensorineural hearing loss. Depending on the presence or absence of certain phenotypic variations, WS was further divided into 4 main types (WS1, WS2, WS3, and WS4) according to the Arias classification in 1971, whereas identification of genetic mutations subdivided some of these types such as types 2A to 2E and types 4A to 4C.

In his first report of the syndrome in 1951, Petrus Johannes Waardenburg described 6 main features including telecanthus (which differentiates WS1 from WS2), broad nasal root, synophrys, white forelock, various degrees of heterochromia irides, and finally deaf-mutism. Type 3 WS is associated with limb anomalies, mainly of upper limbs while in type 4 the patient suffers from Hirschsprung disease. Most types of WS show autosomal dominant inheritance with some showing autosomal recessive pattern.

Additional ophthalmic features that have been recorded include various degrees of fundus depigmentation, refractive errors, and glaucoma. The latter has been reported in some patients, including the first patient, yet it has never been classified as one of the features of the disease. Whether it is an association or a mere coincidence is yet to be determined through detailed studying of a large series of patients which is difficult due to the rare nature of the disease (estimated prevalence of about 1 in 42,000). Glaucomas in previous WS patients’ reports were of open-angle glaucoma in adults. Here we report a case of juvenile open-angle glaucoma (JOAG) in a 20-year-old man with WS which, to date, has never been reported before.

CASE REPORT

A 20-year-old Egyptian man presented in August 2019 with left diminution of vision. Ocular examination revealed a refraction of −11.75−2.50 at 95 degrees in the right eye and −13.75−2.0 at 105 degrees in the left eye. His best-corrected visual acuities were 0.8 and 0.05 in his right and left eyes, respectively. The intraocular pressures (IOP) measured by Goldmann applanation tonometry were 18 and 20 mm Hg on topical antiglaucoma medications (carbamic anhydrase inhibitor, beta-blocker, prostaglandin analogue, and alpha-agonist). Anterior segment examination revealed clear corneas, deep clear ante- chronic irides with bilateral asymmetrical superior sectoral irides hypopigmentation which was broader in the left eye with a prominent iris blood vessel at 12 o’clock in the right eye as shown in Figures 1A and B. Gonioscopy revealed hypopigmented trabecular meshwork and generally open angles (Fig. 2A), which was expected with such degrees of myopia that the patient had, with some embryonic features in some quadrants in the form of high iris insertion obscuring the trabecular meshwork and pathologic long iris processes (Fig. 2B). The quadrants of significantly hypopigmented trabecular meshwork coincided with the sectors of iris hypochromia (superiorly). Dilated examination revealed bilateral clear lenses and advanced glaucomatous cupping of almost 1.0. Both fundi were of albinotic appearance with diffuse hypopigmentation throughout the choroid without localized areas of selective color changes.

Systemic history taking revealed congenital, profound, bilateral sensorineural hearing loss with zero repeat diminution resulting in a deaf-mute state. There was no history of any neurological or gastrointestinal problems. The patient denied steroids intake as well as previous ocular trauma or surgery. Apart from a positive family history of glaucoma in the father only, there were no other family members with known history of glaucoma or phenotypic features suggestive of WS which agrees with the de novo mutation patterns seen in some of the families of affected patients. On systemic examination, there were no signs of skin or hair hypopigmentation or hyperpigmentation or any limb structural anomalies. Taking into consideration the sensorineural hearing loss, the striking sectoral irides pigmentary defects and the lack of telecanthus and intestinal malformations, a diagnosis of WS2 was reached. The high myopia does not come as a surprise in this patient since different refractive errors have been described with the syndrome including anisometropia, astigmatism, and high myopic errors associated with albinotic fundi. The superior sectoral irides hypopigmentation have been recorded before in the literature and in some of the cases was associated with a superior corresponding sector of choroidal depigmentation. In our case, it was the superior angle that showed similar pigmentary defects and not the choroid. The patient’s glaucoma was categorized as JOAG owing to the age of presentation, the lack of features suggestive of congenital glaucoma such as megalocorneas and Haab’s striae and the absence of any cause for secondary glaucoma such as inflammation, steroids or trauma. Also, the embryonic-like features of some quadrants on gonioscopy agrees with angle anomalies seen in a subset of JOAG patients.

The patient was scheduled for sequential nonpenetrating sutureless deep sclerectomy surgeries in both eyes which were uneventful. Postoperative IOPs have been stable since the surgeries...
at an average of 18 and 16 mm Hg in the right and left eyes respectively on prostaglandin analogue drops.

DISCUSSION

WS is caused by genetic mutations that affect the division and migration of Neural Crest Cells (NCCs) during embryonic stages of development. The NCCs give rise to melanocytes as well as structures in the inner ear, cartilage, and bone. Type 1 of WS, which is the most common type, is caused by mutations of the PAX3 gene resulting in telecanthus, complete or sectoral heterochromia iridum (giving characteristic bright blue appearance), high nasal bridge, flat tipped nose, small alae of nostrils, unibrow, and patches of skin depigmentation. According to the criteria needed for diagnosis of WS, our patient has 2 major criteria and lacks the abnormal increased distance between both medial canthi which categorizes him as WS2, the second most common type of WS. Most of these cases are caused by a mutation in MITF gene where sensorineural hearing loss is more common and more profound compared with WS1. Reports of WS2 due to mutations of SOX10 gene described patients with multiple neurological deficits such as nystagmus and muscle tone anomalies which were not present in the patient discussed here. Type 3 of WS, also known as Klein-Waardenburg syndrome, represents a more severe form of WS1 PAX3 gene mutation characterized by prominent limb and muscular anomalies in addition to microcephaly and developmental delays. Type 4 WS, Shah-Waardenburg Syndrome, is the least common form in which there is congenital lack of intestinal nerves leading to bowel dysfunction.

Glaucoma has not been listed as one of the main findings in WS. On reviewing the literature, there has been previous reports of open-angle glaucomas in adult WS patients but there has been no reports of JOAG in association with WS. JOAG is known to be associated with positive family history of glaucoma and an early age of onset beyond the age of 5 years which explains the absence of buphthalmos findings seen in congenital glaucomas. The patient discussed in this report presented late with diminution of vision due to advanced cupping from prolonged periods of elevated IOP which is very characteristic of JOAG patients. The insidious onset and asymptomatic nature of the disease make routine, regular full ophthalmological examination of children mandatory for early detection of the disease. Gonioscopic examination of JOAG is usually normal, yet anomalies such as long iris processes with dysplastic trabecular meshwork can be occasionally seen like the patient described above. Unlike the primary open-angle glaucoma seen in adults, surgical reduction of the IOP is the ultimate solution for persistently elevated IOP in JOAG where medical therapy represents a temporary measure til the date of the surgery. Nonpenetrating deep sclerectomy in such patients has been proven to be successful in controlling the IOP while avoiding
the hypotony and bleb-related complications seen with trabeculectomy in young patients.\textsuperscript{31} The patient was referred for genetic counselling.

To date, gene mutations affecting the MYOC\textsuperscript{32,33} and CYP1B1\textsuperscript{34} genes have been identified as causative factors of JOAG. The genetics behind WS and JOAG are still unraveling. Due to lack of previous reports or studies on both diseases occurring together, it is not known if the 2 disease entities are connected or if it is just a coincidence of 2 unrelated diseases coexisting in the same patient. During embryonic development, NCCs share in the development of the trabecular meshwork.\textsuperscript{35} It is now known that NCCs disruption, which is responsible for phenotypic features of WS,\textsuperscript{1} is also the cause behind development of anterior segment dysgenesis syndromes responsible for phenotypic features of WS.\textsuperscript{1} The modes of inheritance of the 2 diseases (JOAG\textsuperscript{22} of the family suffering from glaucoma or having any features among the affected patients according to different genetic cases revealed a considerable range of phenotypic variations resulting in various degrees of pigmentary albino-like defects and hearing loss. Over the past decades, documentation of reported cases revealed a considerable range of phenotypic variations among the affected patients according to different genetic mutations. Even though it is not a main feature of the disease, yet glaucoma has been reported in several WS cases in the literature, namely bilateral open-angle glaucoma with no secondary cause. In our work, we report a novel finding of JOAG coexisting with signs of WS in a 20-year-old Egyptian man. In any documented WS case, even if it is in the pediatric age group, routine follow-up for IOP monitoring is mandatory for early detection and management of glaucoma if present. JOAG is becoming an increasingly recognized cause of significant optic nerve dysfunction among teenagers due to late presentation.

**CONCLUSION**

WS is a rare genetic disorder affecting the development of neural crest cells during embryonic stages of development resulting in various degrees of pigmentary albino-like defects and hearing loss. Over the past decades, documentation of reported cases revealed a considerable range of phenotypic variations among the affected patients according to different genetic mutations. Even though it is not a main feature of the disease, yet glaucoma has been reported in several WS cases in the literature, namely bilateral open-angle glaucoma with no secondary cause. In our work, we report a novel finding of JOAG coexisting with signs of WS in a 20-year-old Egyptian man. In any documented WS case, even if it is in the pediatric age group, routine follow-up for IOP monitoring is mandatory for early detection and management of glaucoma if present. JOAG is becoming an increasingly recognized cause of significant optic nerve dysfunction among teenagers due to late presentation.

**REFERENCES**

1. Saleem MD. Biology of human melanocyte development, Pigelmat, and Waardenburg syndrome. Pediat Dermatol. 2019;36:72–84.
2. Newton VE. Clinical features of the Waardenburg syndromes. Adv Otorhinolaryngol. 2002;61:201–208.
3. Arias S. Genetic heterogeneity in the Waardenburg syndrome. Birth Defects. 1971;07:87–101.
4. Song J, Feng Y, Acker FR, et al. Hearing loss in Waardenburg syndrome: a systematic review. Clin Genet. 2016;89:416–425.
5. Waardenburg PJ. A new syndrome combining developmental anomalies of the eyelids, eyebrows and nose root with pigmentary anomalies of the iris and head hair and with congenital deafness. Am J Hum Genet. 1951;3:195–253.
6. Goodman RM, Leithal I, Solomon A, et al. Upper limb involvement in the Klein-Waardenburg syndrome. Am J Med Genet. 1982;11:425–433.
7. Shah KN, Dalal SJ, Desai MP, et al. White forelock, pigmentary disorder of irides, and long segment Hirschsprung disease: possible variant of Waardenburg syndrome. J Pediatr. 1981;99:432–435.
8. Julianin N, Tabataibaefar MA, Bahrami T, et al. A novel pathogenic variant in the MITF gene segregating with a unique spectrum of ocular findings in an extended Iranian Waardenburg Syndrome Kindred. Mol Syndromol. 2017;8:195–200.
9. Nasser LS, Paranaiba LM, Frota AC, et al. Waardenburg syndrome—ophthalmic findings and criteria for diagnosis: case reports. Arq Bras Oftalmol. 2012;75:352–355.
10. Bard LA. Heterogeneity in Waardenburg’s syndrome: report of a family with ocular albinism. Arch Ophthalmol. 1978;96:139–1198.
11. Kadoi C, Hayaska S, Yamamoto S. Branch retinal vein occlusion in a patient with Waardenburg syndrome. Ophthali-nologica. 1996;210:354–57.
12. Nork IM, Shihab ZM, Young RSL, et al. Pigment distribution in Waardenburg syndrome: a new hypothesis. Graefes Arch Exp Ophthalmol. 1986;224:487–494.
13. Gupta V, Aggarwal HC. Open angle glaucoma as a manifestation of Waardenburg’s syndrome. Indian J Ophthalmol. 2000;48:49–50.
14. Pingault V, Ente D, Dastot-Le Moal F, et al. Review and update of mutations causing Waardenburg syndrome. Hum Mutat. 2010;31:391–406.
15. Wildhardt G, Zirn B, Graul-Neumann LM, et al. Spectrum of novel mutations found in Waardenburg syndrome types 1 and 2: implications for molecular genetic diagnostics. BMJ Open. 2013;3:e001917.
16. Ma J, Zheng Z, Jiang HC, et al. A novel dominant mutation in the SOX10 gene in a Chinese family with Waardenburg syndrome type II. Mol Med Rep. 2019;19:1775–1780.
17. Kozawa M, Kondo H, Tahira T, et al. Novel mutation in PAX3 gene in Waardenburg syndrome accompanied by unilateral macular degeneration. Eye. 2009;23:1619–1621.
18. Jorge R, Carvalho RC, Rodrigues MV, et al. Sindrome de Waardenburg: relato de 3 casos associados com alta miopia [Waardenburg syndrome: report of 3 cases with high myopia]. Arq Bras Oftalmol. 1997;60:653–654.
19. Kumawat D, Kumar V, Sahay P, et al. Bilateral asymmetrical partial heterochromia of iris and fundus in Waardenburg syndrome type 2A with a novel MITF gene mutation. Indian J Ophthalmol. 2019;67:1481–1483.
20. Rishi P, Multani P, Prasan VV, et al. Choroidal thickness in Waardenburg syndrome. GMS Ophthalmol Cases. 2019;9:22.
21. Babich AE, Bradfield YS. Diagnosis and management of juvenile open-angle glaucoma. In: Traboulssi EU, ed. Practical Management of Pediatric Ocular Disorders and Strabismus. New York, NY: Springer; 2016:471–497.
22. Wiggs JL, Del Bono EA, Schuman JS, et al. Clinical features of five pedigrees genetically linked to the juvenile glaucoma locus on chromosome 1q21-q31. Ophthalmology. 1995;102:1782–1789.
23. Gupta V, Srivastava RM, Rao A, et al. Clinical correlates to the congenital anomalies of the eyelids, eyebrows and nose root with pigmentary disorder of irides, and long segment Hirschsprung disease: possible variant of Waardenburg syndrome. Graefes Arch Exp Ophthalmol. 2013;251:1571–1576.
24. O’Rahilly R, Müller F. The development of the neural crest in the human. J Anat. 2007;211:335–351.
25. Read AP, Newton VE. Waardenburg syndrome. J Med Genet. 1997;34:656–665.
26. Farrer LA, Grundfast KM, Amos J, et al. Waardenburg syndrome (WS) type I is caused by defects at multiple loci, one of which is near ALPP on chromosome 2: first report of the WS consortium. Am J Hum Genet. 1992;50:902–908.
27. Yang T, Li X, Huang Q, et al. Double heterozygous mutations of MITF and PAX3 result in Waardenburg syndrome: a systematic review. Mol Syndromol. 2017;8:195–200.
28. Milunsky JM, Waardenburg syndrome type I. In: Adam MP, Arndt HH, Pagon RA, et al. GeneReviews®. Seattle, WA: University of Washington; 2001:1993–2020.
29. Kwun Y, Lee EJ, Han JC, et al. Clinical characteristics of juvenile-onset open angle glaucoma. Korean J Ophthalmol. 2016;30:127–133.
30. Al-Obeidan SA, Mousa A, Naseem A, et al. Efficacy and safety of non-penetrating deep sclerectomy surgery in Saudi patients with uncontrolled open angle glaucoma. *Saudi Med J*. 2013;34:54–61.

31. Tsai JC, Chang HW, Kao CN, et al. Trabeculectomy with mitomycin C versus trabeculectomy alone for juvenile primary open-angle glaucoma. *Ophthalmologica*. 2003;217:24–30.

32. Wiggs JL, Lynch S, Ynagi G, et al. A genomewide scan identifies novel early-onset primary open-angle glaucoma loci on 9q22 and 20p12. *Am J Hum Genet*. 2004;74:1314–20.

33. Sunden SL, Alward WL, Nichols BE, et al. Fine mapping of the autosomal dominant juvenile open angle glaucoma (GLC1A) region and evaluation of candidate genes. *Genome Res*. 1996;6:862–869.

34. Acharya M, Mookherjee S, Bhattacharjee A, et al. Primary role of CYP1B1 in Indian juvenile-onset POAG patients. *Mol Vis*. 2006;12:399–404.

35. Tripathi BJ, Tripathi RC. Neural crest origin of human trabecular meshwork and its implications for the pathogenesis of glaucoma. *Am J Ophthalmol*. 1989;107:583–590.