• Letter to the Editor •

Association of type II Waardenburg syndrome with hypermetropic amblyopia

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Dear Editor,

We present a case of hypermetropic amblyopia in type II Waardenburg syndrome (WS) to highlight the association. WS is an "oculo-dermato-auditif" dysplasia described in 1947 by Waardenburg and by Klein in 1950. It is distributed worldwide, with no predilection for race or gender. The prevalence is estimated to be 1:42 000 live births in the general population[1-2]. WS is a genetic disease with autosomal dominant transmission with incomplete penetrance and variable expressivity. Complex network of interaction between six genes have been identified to date. They are *PAX3* gene, primarily responsible for type I and III WS; *MITF*, *SOX10*, and *SNAI2* genes in type II WS; *EDN3* and *EDNRB* genes in type IV WS[1-4].

Patients living with WS can present with telecanthus, broad nasal root, synophrys of eyebrows, white forelock, heterochromia iridis and deaf-mutism. WS is classified into 4 types. Type I presents the full symptomatology with canthorum dystopia while type II has no canthorum dystopia. Type III WS includes type I WS with musculoskeletal abnormalities or ortho-osteo-myo-dysplasia of the upper limbs. Type IV WS (Shah-Waardenburg syndrome) includes type I WS with congenital megacolon[1-2,4].

The diagnostic criteria for WS have been proposed by the Waardenburg Consortium in Table 1. It includes at least 2 major criteria or 1 major plus 2 minor criteria. The categorization of WS (I to IV) can be established by clinical features. Molecular genetic analysis can aid in the diagnosis if the clinical features are inconclusive. Our patient has 2 major criteria met without canthorum dystopia and hence classified as type II WS[1-2,4]. We obtained the written informed consent from the patient's parent, and this case study is in accordance with the tenets of the Declaration of Helsinki.

This is a returned case of 11-year-old girl diagnosed with type II WS since the age of five months with bilateral sensorineural hearing loss, heterochromia iridis and a family history of deafness. She underwent a cochlear transplant at three years old. She had her first ophthalmology assessment at three years old with an objective refractive assessment documented as bilateral best corrected visual acuity (BCVA) of 20/30 and hypermetropia of +3.00 spherical diopter (+3.00 D).

However, she defaulted the ophthalmology follow up until she presented again at the age of 11 years old complaining of bilateral suboptimal vision. A detailed ophthalmic examination revealed both eyes hypermetropic amblyopia with right eye BCVA 20/40, +3.75 D and left eye BCVA 20/40, +3.50 D. Anterior segment examination revealed heterochromia iridis with right eye hypochromia as previously documented (Figure 1). Dilated fundus examination showed bilateral mixed hypo- and hyperpigmentation of the fovea and peripheral retina (Figure 2A, 2B). Other examinations were unremarkable. There was no other feature of WS such as white forelock or telecanthus. She had no squint, anisocoria or reactive afferent pupillary defect. The optic discs were pink with cup-to-disc ratio of 0.3. She was prescribed with glasses with regular follow up for reassessment.

Her BCVA remained 20/40 in the right eye and 20/60 in the left eye after 3y of follow up. There was no other new ocular finding except some further pigmentary changes in the peripheral retina (Figure 2C, 2D).

Table 1 Diagnostic criteria for Waardenburg syndrome[1,5]

Rank	Criteria
Major	Congenital sensorineural hearing loss White forelock, hair hypopigmentation Iris pigmentation abnormality: complete heterochromia iridum, segmental heterochromia, or complete hypoplastic blue iridis (brilliant blue iridis) Dystopia canthorum, [a]W index>1.95 Affected first-degree relative
Minor	Skin hypopigmentation (congenital leukoderma) Synophrys/medial eyebrow flare Broad high nasal root, prominent columella Hypoplastic nasal alae Premature gray hair (age<30y)

[a]W index, W=X+Y+a/b. The measurements necessary to calculate the W index (in millimeters) are: inner canthal distance (a), interpupillary distance (b), and outer canthal distance (c). X=[2a-(0.2119c+3.909)]/c. Y=[2a-(0.2479b+3.909]/b.

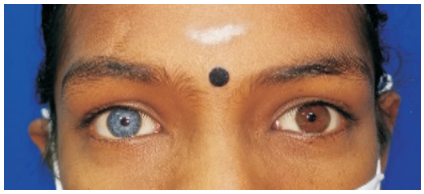

Figure 1 Heterochromic iridis with right eye hypochromia, absent of white forelock.

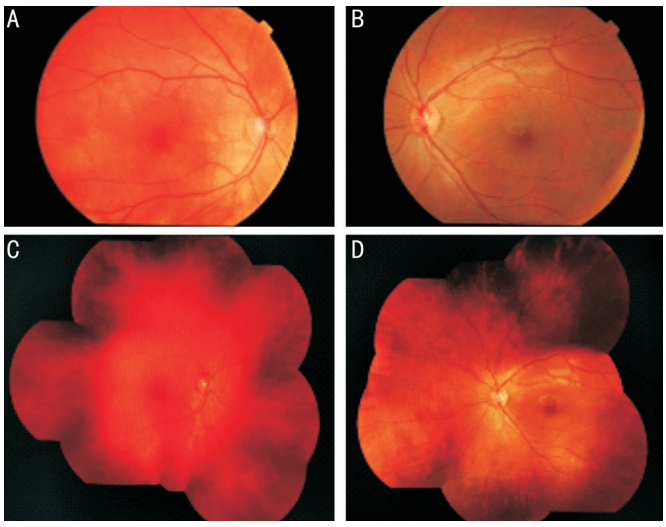

Figure 2 Pigmentary changes A, B: Fundus photo showed bilateral mixed hypo- and hyperpigmentary changes of the fovea at 11 years old; C, D: Collage fundus photo showed bilateral eyes with increased pigmentary changes of the fovea and peripheral retina after 3y of follow up.

Literature search with the words "Waardenburg syndrome" AND "amblyopia" and its related terms using PubMed Medline, EBSCOhost Medline, and Scopus databases revealed seven reports with total of 12 cases, which are summarized in Table 2[1,3,5-7].

Akal *et al*[5] reported a case of type II WS with anisometropic amblyopia. Reported case had left eye hypermetropia with BCVA 0.3. After occlusion therapy for amblyopia, the left eye BCVA improved to 0.4. The author drew attention for detailed ophthalmology examination in type II WS and amblyopia should be investigated, to avoid delay in diagnosis and treatment of additional pathologies.

Ohno *et al*[3] reported a cases series involving 11 patients with type II WS and only two patient had a unilateral hypermetropic amblyopia. The rest of the patients had no poor vision or visual field defects.

Albarry *et al*[1] studied a Saudi family with eleven members diagnosed with type II WS. Two of the family members had bilateral amblyopia and another two of the family members had unilateral amblyopia. They postulated that amblyopia is related to hypopigmentation of the fundus in the four families as there were no other fundus abnormalities found.

Similar to Sharma and Arora's[4] report, the author reported two cases of type II WS. One of the patients had amblyopia and the author also associated the amblyopia to the fundus depigmentation.

Cortés-González *et al*[8] studied two unrelated families with WS. The author reported that among all type II WS patients, one had bilateral reduced anteroposterior axial length (AP-AXL) and a high hypermetropic refractive error corresponding to posterior microphthalmos. The author also reported in the first family, there were 3 patients with hypermetropia and 2 of them had reduced AP-AXL; and in the second family, one patient had hypermetropia with reduced AP-AXL. However, the visual acuities were not reported.

Read and Newton[2] showed that there is an association between mutation of the *MITF* gene with microphthalmia in type II WS. The author explained that *MITF* gene, the human homologues of the mouse microphthalmia gene is mapped to the same location. This explained the association of hypermetropic refractive error with reduced AP-AXL in Vianney's report.

Falzon *et al*[9] reported that 42% of 141 children who had undergone cochlear implant had ocular abnormalities with refractive errors. Hypermetropia was the most common refractive error (15%) and one of the children was diagnosed with WS.

Table 2 Summary of systematic literature review

Literature	Total No. of WS cases	No. of cases with amblyopia	Amblyopia cases	Refractive status and visual acuity of amblyopic eye (s)		Other ocular findings
				Right eye (OD)	Left eye (OS)	
Akal *et al*[5], 2013	1	1	8y/male hyperopic amblyopia	BCVA 1.0 +5.00 D	BCVA 0.3 +6.50 D	OD: Segmental heterochromia. Fundus unremarkable OS: Complete heterochromia. Fundus unremarkable
Ohno *et al*[3], 2003	11	2	18y/female hyperopic amblyopia	BCVA 0.9	BCVA 1.2	OD: Segmental heterochromia. Fundus hypopigmentation in upper temporal periphery OS: Complete heterochromia. Fundus total hypopigmentation
			15y/female hyperopic amblyopia	BCVA 1.0	BCVA 0.7	OD: Complete heterochromia. Fundus total hypopigmentation OS: Segmental heterochromia. Fundus total hypopigmentation
Bard[6], 1978	7	4	12y/female hyperopic amblyopia	BCVA 20/30 +2.25 D	BCVA 20/40 +3.75 D	OD: No iris hypopigmentation. Fundus segmental hypopigmentation OS: Segmental heterochromia. Fundus more segmental hypopigmentation compare to right eye
			10y/female hyperopic amblyopia	BCVA 20/40 +4.50 D	BCVA 20/30 +4.62 D	OD: No iris hypopigmentation. Fundus peripheral hypopigmentation OS: Segmental heterochromia. Fundus more peripheral hypopigmentation compare to right eye
			7y/female hyperopic amblyopia	BCVA 20/40 +3.00 D	BCVA 20/50 +3.25 D	Both eyes: Complete heterochromia. Fundus albinotic
			7y/male hyperopic amblyopia	BCVA 20/30 +1.50 D	BCVA 20/200 +7.00 D	OD: Segmental heterochromia. Fundus macula albinotic, segmental hypopigmentation and white spots OS: Segmental heterochromia. Fundus mottled yellow maculae, segmental hypopigmentation and tilted disc
Li *et al*[7], 2019	Total 90. 57 are type 2 WS	1		NA	NA	Iris heterochromia.
Albarry *et al*[1], 2019	11	4	58y/male amblyopia	BCVA 0.9	BCVA 0.7	Both eyes heterochromia. Fundus hypopigmentation
			16y/male amblyopia	BCVA 0.6	BCVA 0.4	OD: No abnormality OS: Segmental heterochromia. Fundus generalised hypopigmentation
			28y/female amblyopia	BCVA 0.8	BCVA 0.7	OD: Segmental heterochromia. Fundus no hypopigmentation OS: Segmental heterochromia. Fundus generalised hypopigmentation
			25y/female esotropia amblyopia	NA due to mentally retard	NA due to mentally retard	Both eyes no abnormality

BCVA: Best corrected visual acuity; NA: Not available.

Refractive error and amblyopia are not typically present in WS and are not included in the latest diagnostic criteria of the disease. However, our literature review revealed 12 cases of amblyopia and 7 of them were related to refractive error and all of the 7 cases were hypermetropia. The hypermetropic power ranged from +2.25 D to +6.50 D. None of the reports documented repeated refraction. We believe the true incidence of hypermetropic amblyopia is unknown due to the lack of formal and serial refractive assessment in the previous reports. There were other causes of amblyopia reported from the literature review. Three cases were postulated that amblyopia is related to hypopigmentation of fundus. Six out of 7 cases reported of hypermetropic amblyopia had hypopigmented fundus as well. The remaining 2 cases did not explain the cause of amblyopia. Our patient does have macula hypopigmentation as well. However, patient with hypopigmentation of retinal

pigment epithelium without macular hypoplasia may not related to reduced visual acuity[3].

Our case report revealed an interesting finding of persistent hypermetropia that documented from age of 3 to 11. None of the previous reported cases documented this persistent hypermetropia. The failure of emmetropization showed in this case can be related to the underlying genetic problem in WS. The underlying deranged melanocytic-pigmentary system in WS may lead to disruption of normal emmetropization as suggested by previous studies on ocular albinism[2,6], which leads them to the risk of persistent hypermetropia and subsequently development of amblyopia if untreated.

Refractive hypermetropia is well known to cause amblyopia, but an association between WS and refractive amblyopia due to failure of emmetropization has not been made. This might draw the attention of eye care providers to this association and to be aware that detailed ophthalmic and refractive examinations in patients with WS may prevent refractive amblyopia.

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