Case study

Blue-Eyed Asian: A Case Report of Waardenburg Syndrome Type 1

ABSTRACT

Aims: To report a case of Waardenburg Syndrome Type 1 presenting with bilateral blue iris in a young Asian.
Presentation of Case: A 7-year old Filipino girl was referred for ophthalmologic evaluation for bilateral blue eyes. She also presented with an eyebrow flare, broad nasal root, dystopia canthorum, heterochromic fundi and mild hearing loss. Her medical, developmental and family histories were unremarkable.
Discussion: Waardenburg Syndrome is a rare clinical disorder with oculocutaneous pigmentary anomalies, deafness and dystopia canthorum as major features. Diagnosed clinically using a Consortium criteria, this is one of the differential diagnoses when presented with a patient with bilateral blue eyes. There have been reports of this disorder in Asia but there are no known published articles or cases from the Philippines.
Conclusion: This is the first reported case of Waardenburg Syndrome in the country. This case presented with an atypical combination of bilateral blue eyes and heterochromic fundi in a young Asian girl.

Keywords: Waardenburg syndrome, Blue iris, Pale blue eyes, Heterochromic iris, Heterochromic fundi, PAX gene, Dystopia canthorum, Hearing loss

1. INTRODUCTION

Waardenburg Syndrome (WS), first published in 1951 by a Dutch ophthalmologist, is a rare genetic disorder with associated pigmentary anomalies of the hair, skin, eyes and minimal facial abnormalities, and congenital sensorineural deafness [1,2]. It approximately affects 1:40,000 population and comprises 3% of congenitally deaf children. It has no racial or ethnic predilection and with equal male to female ratio [3,4]. There have been reports of WS in Asia (e.g. Korea, India, Tokyo) but there are no known published articles or cases of the syndrome from the Philippines.

This syndrome is genetically and clinically heterogeneous, with four subtypes. WS Type1 (WS1) can be diagnosed using the WS Consortium Diagnostic Criteria (Table 1), with 2 major or 1 major plus 2 minor features fulfilled [1-6]. Type 2 lacks dystopia canthorum or the lateral displacement of the medial canthi. Type 3 is a severe form of WS Type1 with associated limb defects. Type 4 is characterized by Hirschsprung disease [2,7]. The characteristic features of WS1 are dystopia, broad and high nasal root, synophrys, partial or total heterochromic iris, white forelock and congenital deaf-mutism [7].

This is a case of a young Filipino girl, of pure Mangyan lineage, with an atypical WS1 presentation of bilateral blue iris and heterochromic fundi. This is the first known reported case of WS in the country.

Table1. Waardenburg Syndrome Consortium Diagnostic Criteria

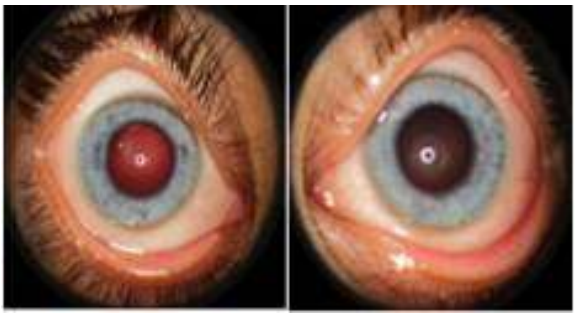
Major Criteria	Minor Criteria

• Congenital sensorineural hearing loss
• White forelock, hair hypopigmentation
• Pigmentation abnormality of the iris
  o Complete heterochromia iridum
  o Partial/segmental heterochromia
  o Hypoplastic blue irides or brilliant blue eyes
• Dystopia canthorum, Waardenburg index (W index) >1.95
• Affected first degree relative
	• Skin hypopigmentation (congenital leukoderma)
	• Synophrys/medial eyebrow flare
	• Broad/high nasal root, prominent columella
	• Hypoplastic alae nasi
	• Premature gray hair (age <30 years)

2. PRESENTATION OF CASE

A 7-year old girl from the Mangyan indigenous people of Mindoro Island in the Philippines was referred for ophthalmologic evaluation because of bilateral blue eyes. Based on interview and examination conducted by the authors in Manila, her prenatal, birth and developmental histories are unremarkable, with no history of medical illness or ototoxic drug intake. She is the second of three children of a non-consanguineous marriage. Family history is unremarkable. On physical examination, she has slim built with no facial, abdominal or limb anomalies. She presents with bilateral pale blue eyes, mild eyebrow flare and a broad nasal root (Fig. 1 and 2), with no skin and hair pigment anomalies seen anywhere in her body.

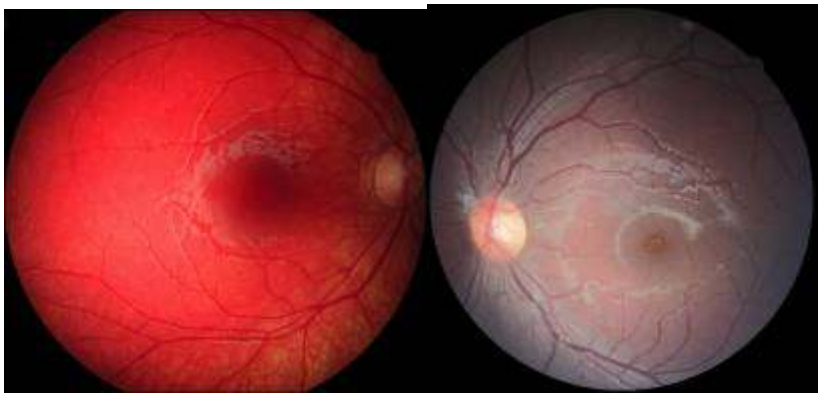
Figure 1. Photograph showing the facial features of bilateral pale blue eyes, mild eyebrow flare, and broad nasal root.



A. Right eye **B. Left eye**

Figure 2. Photos show both eyes with pale hypochromic color

Measurements for inner intercanthal, outer intercanthal and interpupillary distance were 31mm, 78mm and 52mm respectively, with a computed W index of 2.0 for dystopia canthorum. Ophthalmologic examination revealed best corrected visual acuity of 20/25 OD and 20/30 OS, with 3mm equally brisk reactive pupils, no nystagmus and relative afferent pupillary defects (RAPD). Cycloplegic refraction for OD is +1.00 D sph with -1.00 D cyl x180 and OS is +1.00 D sph. Extraocular muscles were full OU. Slit lamp findings OU showed formed chambers, clear cornea and lens, bilateral pale blue iris with no transillumination defects. Intraocular pressure OU was 10mmHg. Fundus examination demonstrated a heterochromic fundi with the right being hypopigmented and the left showing normal fundus color (Fig. 3).



A. Right eye **B. Left eye**

Figure 3. Fundus of the right eye (A) shows hypopigmentation while the left eye (B) has a normal fundus color.

Optical Coherence Tomography (OCT) was normal OU. Ear examination showed otoscopically normal findings, however, hearing test (play audiometry) revealed bilateral mild hearing loss. A pedigree was constructed for this index patient (Fig. 4), which showed no similar iris findings in the family. There are no known interracial marriages in the family. The evaluation of the family members was not performed due to inaccessibility and financial constraints. No genetic work-up was done. A clinical diagnosis of Waardenburg Syndrome Type1 was made based on its fulfillment of the Waardenburg Consortium Criteria for the said disease.

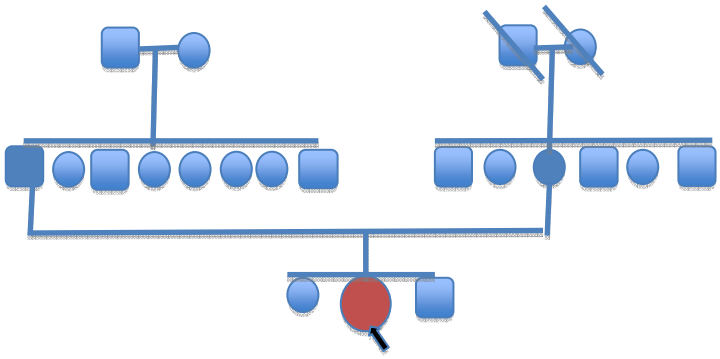


Figure 4. Family Genogram of the Index patient

3. DISCUSSION

Waardenburg Syndrome is a rare disorder characterized with oculocutaneous anomalous pigmentations, deafness and dystopia canthorum, and abnormalities of neural crest derived tissues and its derivatives [2,3,5,7]. This syndrome is clinically heterogeneous and expression of findings is extremely variable, even within a family, thus the WS Consortium was created [2,3]. Using the criteria in this case, the index patient fulfilled 2 major (hypoplastic blue iris, dystopia canthorum) and 2 minor (mild synophrys, broad nasal root) features, establishing the diagnosis of WS. The finding of dystopia canthorum and the absence of limb defects and Hirschsprung disease narrows this to Type 1 WS. The finding of bilateral mild hearing loss in the patient needs further testing (pure tone audiometry) to establish if it is sensorineural or of conductive origin, the latter being the feature of WS.

The bilateral blue iris is the most prominent feature in this patient. According to a 2014 report by Milunsky, the hypoplastic blue irides feature of WS patients is seen in only 15-18%, whereas the more common heterochromic irides is seen in up to 31% of patients. These iris discolorations are rarely seen in non-Waardenburg patients [3,8]. A histopathological study of the blue iris of WS patients showed reduced numbers of stromal melanocytes and smaller melanosomes compared to the fellow brown eye [9]. In Filipinos, of no known genetic disorders, and no interracial marriages, iris colors are gray or black. The differential diagnoses for bilateral blue eyes are ocular/oculocutaneous albinism, Fragile X syndrome, Angelman Syndrome, Prader-Willi Syndrome and Sturge Weber Syndrome. Ocular/oculocutaneous albinism was ruled out since the patient does not have iris transillumination defects, nystagmus and cutaneous hypopigmentations. The absence of mental retardation or disability, unusual facies, and the patient's female sex has ruled out the rest of the diseases mentioned [10,11].

Among the clinical findings of WS, dystopia canthorum is the most penetrant feature of WS1, found in 99% of cases [2]. Dystopia canthorum is the lateral displacement of the medial canthi, and is confirmed when the W index exceeds 1.95 [3]. This can be computed with the following formula:

$X = (2a - (0.2119c + 3.909)) / c$	*where a = inner canthal distance (ICD), in mm
$Y = (2a – (0.2479b + 3.909)) / b$	b = the interpupillary distance (IPD), in mm
$W = X+Y+ a/b$	c = the outer canthal distance (OCD), in mm

The patient's cephalometric measurements are ICD= 31mm, IPD= 52mm and OCD=78mm. Comparing this to an age-based table of cephalometrics, using the Feingold and Bossert table [10], her IPD is within the 25-50 percentile; OCD is within 50-75 percentile, whereas her ICD is high at the 75 percentile. Also using these measurements, the computed W index of the patient is 2.0, confirming the presence of dystopia canthorum.

The medial eyebrow flare or synophrys is seen mildly in the index patient. This feature is usually seen in 63-73% of WS patients. The classic white forelock, early graying of hair and skin hypopigmentations or leukoderma are absent in the patient. These are frequently seen in up to 48%, 38%, 36% of patients respectively [2,3]. The patient's heterochromic fundi, has been reported in some WS patients [7,8]. In a study by Ohno et al in Japan, two of their 11 patients presented with a combination of a normal and a hypopigmented fundi [12].

The most serious symptom in the clinical findings of patient with WS is hearing loss, seen in 47-58%. This is characterized as congenital, sensorineural type, typically non progressive, unilateral or bilateral. The hearing impairment may range from mild to profound, the latter

may require deaf school attendance. This becomes an important prognostic factor because of possible impairment in the quality of life and cognitive abilities of the patient [1,3]. Silan et al screened 720 children with hearing deficits attending special schools in Turkey, and found 49 (6.8%) with WS. All were previously misdiagnosed to have a nonsyndromic deafness [13]. In Japan, a screening of 240 children attending a school for hearing impairment showed 11 (4.6%) with WS Type 2 [12]. The hearing loss is due to the lack of melanocytes in the stria vascularis of the cochlea [5] .

Multiple genes have been implicated in Waardenburg syndrome, but the PAX3 with its pathogenic variants, is the only gene known to cause WS Type 1, in up to 90% of those who meet the diagnostic criteria. Inheritance of this syndrome is by autosomal dominance, with majority of the probands with affected parents. A minority, with mutation rate of 0.4 per 100,000, does not have an affected parent, and may be presumed to be a *de novo* mutation, as in the index patient [3]. An apparent negative family history cannot fully rule out WS until proper clinical evaluation and audiogram of the parents are done which may reveal milder or subtle phenotypic findings. The index patient has an unremarkable family history, however, no formal evaluation/examination of the patient's parents and siblings was done, and is therefore suggested.

Molecular genetic testing is used to confirm the diagnosis of WS Type 1, as well as aid in the early detection and risk of family members of a patient. A child of a WS1 individual has a 50% risk of inheriting the pathogenic gene, however the clinical manifestations cannot be predicted and may range from subclinical to the classic features of the syndrome type. A PAX3 pathogenic variant in one of the proband's parents increases the risk of the siblings to 50% whereas a negative variant for both parents puts the risk to low [3]. Genetic work-up was not conducted in this patient and her parents due to financial constraints, and is recommended to confirm the diagnosis of Waardenburg Syndrome Type1 and to guide in the proper genetic counseling needed in this case.

4. CONCLUSION

We have presented a case of a young Asian- Filipino girl with congenital bilateral blue iris, mild synophrys, dystopia canthorum, heterochromic fundi and mild congenital bilateral hearing loss, which fulfills the criteria for the diagnosis of Waardenburg Syndrome Type1. This is an atypical presentation of the disorder with combination of bilateral blue eyes and heterochromic fundi, which was rarely seen in the review of literature. A genetic work-up of the patient and her parents and full evaluation of the latter are recommended to fully assess the extent and phenotypic-genetic correlations of this case.

CONSENT

All authors declare that written informed consent was obtained from the patient's legal guardian for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editorial office/Chief Editor/Editorial Board members of this journal.

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Ibinibigay ko ang aking pahintulot at permiso na mailahad o mai-*publish* ang mga impormasyon at eksaminasyon tungkol sa aking anak na si MARIEL T. CADAS, na isang menor de edad, pati na ang kanyang mga larawan. Naiintindihan ko na gagamitin ang mga ito at ilalabas sa pahayagan na *Ophthalmology Research: An International Journal* at sa mga kaugnay na pahayagan na walang limitasyon sa tagal ng *publication* o paglalahad.

Naiintindihan ko na ang pangalan niya ay hinde babanggitin at bawat pagsisikap ay gagawin upang panatilihin na *anonymous* ang anak ko sa teksto at sa anumang larawan sa pahayagan. Gayunpaman, naiintindihan ko na ang kumpletong pagka-*anonymous* at kontrol sa paggamit ay hinde garantisado.

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