A Case Study of Two Siblings of Waardenburg Syndrome

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Summary

Waardenburg syndrome is a rare genetically heterogenous disorder of neural crest cell development. Six distinctive features comprising this syndrome include: (1) telecanthus, (2) broad nasal root, (3) synophrys of the eyebrows, (4) a white forelock, (5) heterochromiairides, and (6) deaf-mutism. Waaredenburg syndrome has four subtypes ,depending upon clinical presentation. A careful clinical evaluation should be done to differentiate various types of Waardenburg syndrome and other associated auditory- pigmentary syndrome. We here report two cases of classical features of Waardenburg syndrome in siblings.

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Introduction

Waardenburg syndrome (WS) is a rare autosomally inherited and genetically heterogenous disorder of neural crest cell development with an incidence of 1 in 40,000.[1] Waardenburg syndrome is named after a Dutch ophthalmologist, P.J. Waardenburg, who described a syndrome comprising six distinctive features, including (1) telecanthus (lateral displacement of the medial canthus), (2) broad nasal root, (3) synophrys of the eyebrows (low hairline and eyebrows that meet in the centre, (4) a white forelock (premature graying of frontal hair), (5) heterochromia irides, and (6) deaf-mutism.[2] Based on the clinical presentations, four subtypes were subsequently described.[3,4]

- Type I WS (WS1) consists of dystopia canthorum/ telecanthus (lateral displacement of inner canthi of eye due to broad nasal root).
- Type II WS (WS2) lacks the dystopia canthorum.
- Type III WS (WS3) (Klein-Waardenburg syndrome), a severe form of WS1, is associated with upper limb defects (hypoplasia of the musculoskeletal system, flexion contractures, fusion of the carpal bones, winged scapulae and syndactyly).
- Type IV WS (WS4) (Shah-Waardenburg syndrome) is characterized by Hirschsprung disease.

The diagnostic criteria for WS1 must have two major or one major and two minor criteria to be diagnosed as WS1 (Table 1).[5]

Table 1

Major Criteria
Congenital sensorineural hearing loss Pigmentary disturbances of iris: Complete heterochromia iridis, partial segmental heterochromia iridis, hypoplastic blue irides White forelock Dystopia canthorum Affected first degree relative
Minor Criteria
Congenital leukoderma: several areas of hypopigmented skin synophrys/medial eyebrow flare Broad and high nasal root Hypoplasia of alae nasi Premature graying of hair

Identified genetic mutations in the PAX3 gene can lead to WS1 and WS3. Mutations in MITF and SNAI2 lead to WS2. Type 4 WS is related to multiple mutations in SOX10, EDN3, or EDNRB.[6-8]

There are few case reports of Waardenburg syndrome in literature. We report two cases of classical features of Waardenburg syndrome in siblings.

Case 1

An 18 year old girl presented to Eye OPD with blue coloured eyes. She was also having Medial eyebrow flare (synophrys) and wide intercanthal distance (Figure 1). She also had a white forelock with premature graying of hair, which she had coloured with black hair colour along with hypopigmented patches in her hands and feet (Figure 2,3). She had bilateral profound mixed hearing loss of 98.3 dB in the right ear and 96.6 dB in the left ear with broad nasal root. Her IQ was normal and MRI brain the normal. No other associated features were there. On ophthalmic examination, vision was 20/20 in both eyes. There was lateral displacement of the inner canthus of both eyes. She had hypoplastic blue iridis bilaterally. Pupils were mid dilated with normal reaction. Intraocular pressure was normal. Fundus was albinotic in both eyes (Figure 4).

Figure 1: *Showing synophrys and wide intercanthal distance*

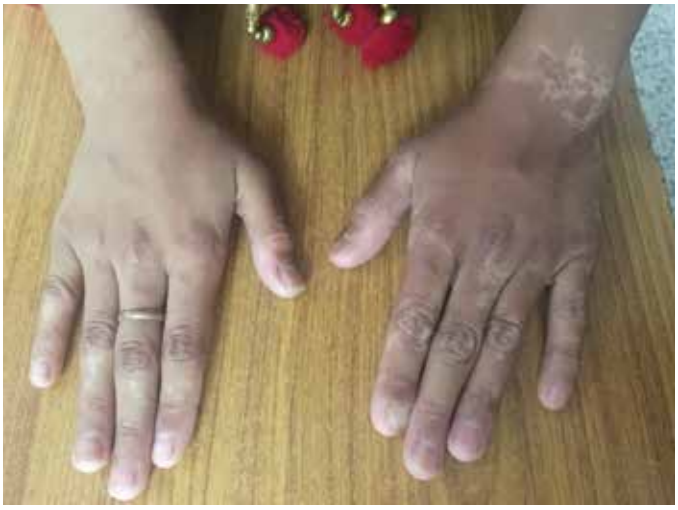

Figure 2: *Showing hypopigmented patches on hands*

Figure 5: *Showing intercanthal distance and hypoplastic blue iridis*

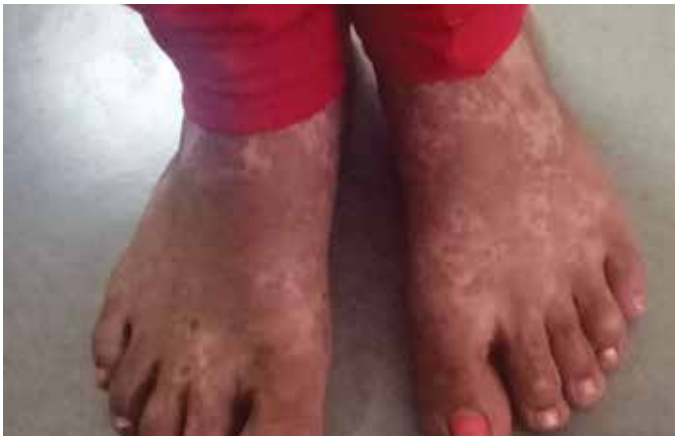

Figure 3: *Showing hypopigmented patches on feet*

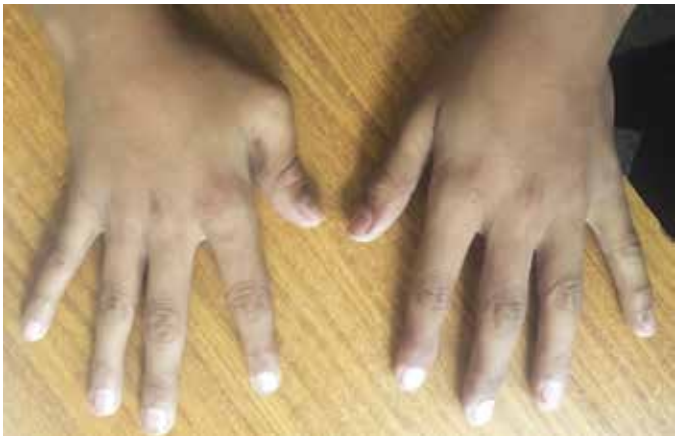

Figure 6: *Showing congenital deformity in right thumb*

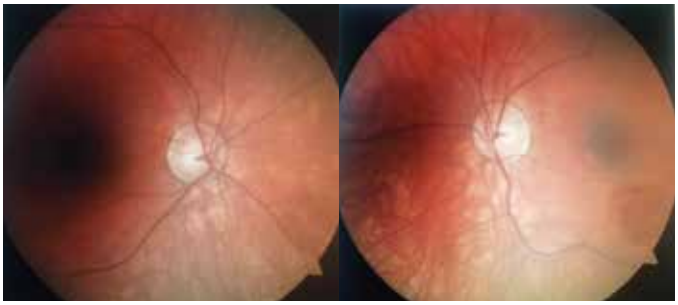

Figure 4: *Showing albinotic fundus*

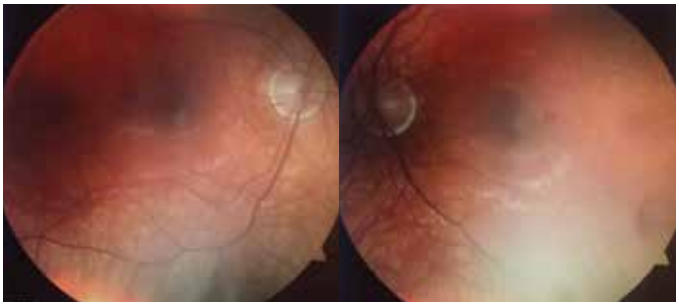

Figure 7: *Showing albinotic fundus*

Case 2

The second patient was her younger sibling who was a 14 year old boy. He had bilateral profound mixed hearing loss of 96.6 dB in the right ear and 98.3 dB in the left ear with a broad nasal root (Figure 5). He had a congenital deformity in his right thumb (Figure 6). His IQ was also normal and MRI brain was normal. On ophthalmic examination, vision was 20/20 in both eyes. There was lateral displacement of the inner canthus of both eyes. He had hypoplastic blue iridis bilaterally. Pupils were mid dilated with normal reaction. Intraocular pressure was normal. Fundus was albinotic in both eyes (Figure 7). Other family members were normal.

Discussion

Waardenburg syndrome varies in its degree of ocular involvement. Identified genetic mutations in the PAX3 gene can lead to WS1 and WS3. Mutations in MITF and SNAI2 lead to WS2.[6,9,10] Type 4WS is related to multiple mutations in SOX10, EDN3, or EDNRB.[6,9-10] Clinical variability is common with WS, even within affected members of a single family. In an analysis of 26 patients diagnosed with WS1, features included telecanthus (82%), white forelock (24%), skin hypopigmentation (30%), iris heterochromia (32%), synophrys (78%), and hypoplastic nasal alae (92%). More severe deafness correlated with more extensive iris

heterochromia.[11] Goldberg stated that the fundus pigmentary abnormalities constituted an integral part of WS.[12] Delleman and Hageman reviewed the ophthalmic findings in WS in 34 patients from 5 families and found 59% (20 of 34) with pigmentary disorders, including 15 with pigmentary iris abnormalities and 3 with hypoplastic blue irides bilaterally. Fundus examination revealed hypopigmentation in 67% (10 of 15) patients.[13] Various studies have shown that there are pigmentary changes in iris, retina and choroid with slight reduction in the thickness of the affected tissue.

Conclusion

Ocular manifestations are an important diagnostic finding in a multitude of genetic syndromes, proper examination is required for evaluating the syndromes. Early diagnosis of this syndrome with appropriate management by hearing aids, appropriate refractive correction, tinted spectacles for photosensitivity can be done for psychological development of children with Waardenburg syndrome.

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