Waardenburg Syndrome: A Case Study of Two Patients

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Abstract Waardenburg syndrome is an autosomal dominant disorder with an incidence of 1 in 40,000 that manifests with sensorineural deafness, pigmentation defects of the skin, hair and iris and various defects of neural crest-derived tissues. This genetically heterogeneous disease accounts for >2 % of the congenitally deaf population. Mutations in the *EDN3*, *EDNRB*, *MITF*, *PAX3*, *SNAI2*, and *SOX10* genes can cause Waardenburg syndrome. We here report a case of 12 year old female who presented with chief complaint of decreased hearing in both ears and had clinical features consistent with Waardenburg syndrome. She had a distinct white forelock of hair in the midline along with striking bilateral blue iris. Also a white depigmented patch was present on the right forearm. Both eyes had bright red fundal reflex with choroidal depigmentation. Her younger brother, the second case in this study, had similar blue eyes, white forelock of hair, depigmented skin patch and choroidal depigmentation but with normal hearing. Their father had a history of premature graying of hair. All the primary care physicians coming across a child with blue eyes and white forelock of hair should get the child's hearing tested at the first instance, if not already tested. An early diagnosis and improvement of hearing impairment with timely intervention are the most important for psychological and intellectual development of children with Waardenburg syndrome.

Keywords Waardenburg syndrome · White forelock · Blue iris · Sensorineural hearing loss

Introduction

Waardenburg syndrome is named after Dutch ophthalmologist Petrus Johannes Waardenburg (1886–1979), who described the syndrome in detail in 1951 [1]. It is an autosomal dominant disorder with an incidence of 1 in 40,000 that manifests with sensorineural deafness, pigmentation defects of the skin, hair and iris and various defects of neural crest-derived tissues [2]. This genetically heterogeneous disease accounts for >2 % of the congenitally deaf population [3]. These auditory-pigmentary syndromes are caused by physical absence of melanocytes from the skin, hair, eyes, or the stria vascularis of the cochlea. Mutations in the *EDN3*, *EDNRB*, *MITF*, *PAX3*, *SNAI2*, and *SOX10* genes can cause Waardenburg syndrome. These genes are involved in the formation and development of several types of cells, including pigment-producing cells called melanocytes. Melanocytes make a pigment called melanin, which contributes to skin, hair, and eye color and plays an essential role in the normal function of the inner ear. Mutations in any of these genes disrupt the normal development of melanocytes, leading to abnormal pigmentation of the skin, hair, and eyes and problems with hearing. Based on the clinical features and the genes involved, WS is classified into four clinical types, namely Type 1, 2, 3 and 4. Types I and III Waardenburg syndrome are caused by mutations in the *PAX3* gene. Mutations in the *MITF* and *SNAI2* genes are responsible for type II Waardenburg syndrome. Mutations in the *SOX10*, *EDN3*, or *EDNRB* genes cause type IV Waardenburg syndrome [4].

We here report two cases from a family, a 12 year old female who presented with chief complaint of bilateral decreased hearing and clinical features consistent with Waardenburg syndrome, and a 5 year old male with clinical features of WS but normal hearing.

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Case Report

A 12 year old girl presented to the ENT OPD with the complaint of decreased hearing in both ears since childhood. She had a distinct white forelock of hair in the midline along with striking bilateral blue iris. Also a white depigmented patch was present on the right forearm (Fig. 1). A diffuse swelling was present in the thyroid region of her neck. Her mother gave the history of prolonged labor and delivery at home associated with a delayed cry at birth and delayed speech development at the age of 6 years. Other developmental milestones were however normal. On asking about family history, it revealed that her younger brother also has similar blue eyes and white forelock of hair and a similar depigmentation of the forearm (Figs. 2, 3). He had white forelock at birth and there was spontaneous shed off of this hair by age of 2 years. Also there is history suggestive of premature graying of hair in her father since the age of 15 years. But none of them had a decreased hearing. Both the children had a normal IQ and go to regular school. Their academic performance is normal.

On investigating the girl, it was found that her pure tone average was 98.33 and 66.66 dB in the right and left ear respectively (Fig. 4). Impedance shows bilateral A type graph. CT scans of the temporal bone revealed a normal external, middle and internal ear. Ultrasound neck showed a diffuse enlargement of isthmus and both lobes of thyroid gland with normal echogenicity and vascularity. No nodules and no enlarged lymph nodes were seen. Her thyroid blood profile showed a hypothyroid picture with TSH 9.78 μ UI/ml. Examination of the eyes showed blue iris.

Fig. 1 Pictures showing distinct white forelock of hair in the *midline*, bilateral blue iris, a white depigmented patch on the *forearm* and a diffuse swelling in the thyroid region of the neck

Fig. 2 Patient's younger brother with similar blue eyes

Visual acuity was 6/6 in both eyes. On fundus examination, a bright red fundal reflex was seen in both eyes. On indirect ophthalmoscopy, there was bilateral choroidal depigmentation perhaps due to visibility of larger choroidal vessels

Fig. 3 Patient and her brother with similar depigmentation of the forearm

especially near the equator (Fig. 5). Macula and optic disc was bilaterally normal.

On investigating the boy, he had a normal hearing threshold with bilateral A type tympanogram. Visual acuity was 6/9 in both eyes. Bilateral choroidal depigmentation was also present along with bright red fundal reflex.

Treatment history: the girl has been fitted with bilateral behind the ear hearing aids and is doing well. She has also been started with thyroxine replacement therapy.

Discussion

Waardenburg syndrome is an autosomal dominant disorder that manifests with sensorineural deafness, pigmentation defects of the skin, hair and iris and various defects of neural crest-derived tissues. These auditory-pigmentary syndromes are caused by physical absence of melanocytes from the skin, hair, eyes, or the stria vascularis of the cochlea. Usually the melanocyte deficiency is patchy, but alternatively a general dilution of pigmentation may be seen. Absence of melanocytes could be because of a failure of differentiation in the neural crest, a failure of melanoblasts to migrate, or a failure to terminally differentiate and survive in their final location. WS2 may be melanocyte specific, whereas WS 1 and the rare variants WS3 and WS4 are neurocristopathies, involving the frontal bone, limb muscles, and enteric ganglia, respectively. All these extra tissues are neural crest derivatives [5].

Mutations in the *EDN3*, *EDNRB*, *MITF*, *PAX3*, *SNAI2*, and *SOX10* genes can cause Waardenburg syndrome. These genes are involved in the formation and development of melanocytes and Mutations in any of these genes can disrupt the normal development of melanocytes, leading to abnormal pigmentation of the skin, hair, and eyes and problems with hearing.

The first patient under study had the following features characteristic of Waardenburg syndrome:

- bilateral sensorineural hearing loss.
- prominent white forelock of hair.
- bilateral blue iris with choroidal depigmentation.
- white depigmented lesion on the arm.
- suggestive family history.

Fig. 4 Pure tone audiogram showing bilateral sensorineural hearing loss

Fig. 5 Bilateral bright red fundal reflex with choroidal depigmentation. Macula and optic disc normal

- younger brother with blue iris and white forelock of hair.
- premature graying of hair in father.

The second patient in this study had the following features consistent with WS:

- white forelock of hair present at birth.
- bilateral blue iris with choroidal depigmentation.
- white depigmented lesion on the arm.
- suggestive family history.

Diagnostic Criteria for WS

According to the diagnostic criteria proposed by the Waardenburg consortium, a person must have two major or one major plus two minor criteria to be diagnosed as WS [6].

Major

- (1) Sensorineural deficit hearing threshold greater than 25 dB for at least two frequencies between 250 and 4000 Hz, without evidence of middle ear effusion and without evidence to suggest that presbycusis or other factors account for the elevated hearing threshold.
- (2) Iris pigmentary abnormality:
 - a. Two eyes of different color.
 - b. Iris bicolor/segmental heterochromia—an eye with two different colors.
 - c. Characteristic brilliant blue (sapphire) iris (alternatively described as “Waardenburg blue eye,” sky-blue eyes, or hypopigmented iris).
- (3) Hair hypopigmentation:
 - a. White forelock: can be present at birth and then disappear later in life, with reappearance in teens or adulthood, or may appear for the first time at any age.
 - b. Body hair: white hairs within eyebrow, eyelashes, or at other sites on the body.

- (4) Dystopia canthorum: Lateral displacement of inner canthi, with a reduction of visible sclera medially.
- (5) First-degree relative diagnosed with WS.

Minor

- (1) Congenital leukoderma—several areas of hypopigmented skin.
- (2) Synophrys or medical eyebrow flare (a flaring or fanning out of the eyebrow hairs medially, toward the nasal bridge).
- (3) Broad high nasal root.
- (4) Hypoplasia of alae nasi—hypoplastic lower lateral cartilages, usually resulting in narrow lower third of the nose.
- (5) Premature graying of the hair—predominance of white scalp hairs before age 30 years.

Rare

- (1) Hirschsprung disease.
- (2) Spina bifida.
- (3) Cleft lip and/or palate.
- (4) Limb defects.
- (5) Congenital heart abnormalities.
- (6) Abnormalities of vestibular function.
- (7) Low anterior hair line.

The first case had 4 major and 1 minor diagnostic criteria present and the second case had 3 major and 1 minor criteria thus establishing the diagnosis of Waardenburg syndrome.

Clinical Types

According to the clinical features and the genes involved, WS is classified into four clinical types, namely Type 1, 2, 3 and 4. Types 3 and 4 are rare compared to types 1 and 2 [4].

Type I Waardenburg syndrome, caused by mutations in the *PAX3* gene, is characterized by evidence of dystopia canthorum and the full symptomatology of the disease. They also have a narrow nose, marked hypoplasia of the nasal bone, short philtrum, and short and retropositioned maxilla.

Type II Waardenburg syndrome is due to mutations in the *MITF* and *SNAI2* genes and is heterogeneous group with normally located canthi (without dystopia canthorum). Sensorineural hearing loss (77 %) and heterochromia iridium (47 %) are the 2 most important diagnostic indicators for this type.

Type III Waardenburg syndrome (Klein-Waardenburg syndrome) is similar to type I but is also associated with musculoskeletal abnormalities.

Type IV Waardenburg syndrome (Shah-Waardenburg syndrome) is the association of Waardenburg syndrome with congenital aganglionic megacolon (Hirschsprung disease). Mutations in the *SOX10*, *EDN3*, or *EDNRB* genes cause type IV Waardenburg syndrome [4, 7].

Thus according to these, both the patients in this report can be diagnosed as case of Waardenburg syndrome Type II.

Conclusion

All the primary care physicians coming across a child with blue eyes and white forelock of hair should get the child's hearing tested at the first instance, if not already done. An early diagnosis and improvement of hearing impairment with timely intervention are the most important for

psychological and intellectual development of children with Waardenburg Syndrome. Genetic and familial counselling is also a good tool for these syndromed patients.

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Conflict of interest All the authors declare that they have no conflict of interest.

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