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Case Report

A rare genetic mutation case report: Waardenburg syndrome type I

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ABSTRACT

Waardenburg syndrome is a rare genetically inherited disorder well-known for its classical auditory-pigmentary abnormalities. Various other minor systemic defects can also occur in structures developing from neural crest cells during embryogenesis. We are reporting a case of a 7-year old girl who presented to our OPD with bilateral sensorineural hearing loss and heterochromia iridis.

1. Introduction

Waardenburg syndrome (WS) is an uncommon autosomally inherited disorder described first time by a Dutch ophthalmologist, P. J. Waardenburg in 1951.[1] It is a heterogeneous genetic disorder characterized by sensorineural deafness along with depigmentary changes and defects in derivatives of neural crest cells. Clinical changes in skin, hair, and eye occur due to the physical absence of melanocytes.[2]

1.1. Genetics

The estimated incidence of WS is 2 per 1 lac without any predilection for race or sex.[3] In about 20% of cases, WS is expressed in the incomplete form.[4] Different genetic mutations like insertion, deletion, frameshift, missense, and nonsense disrupting the normal development of melanocytes. Mutations in the PAX3 gene on chromosome 2q37 are present in WS1 and WS 3. MITF on chromosome 3p12 in WS 2 whereas SOX 10 and Endothelin B receptors (EDNRB) gene is mutated in WS 4 respectively.[5,6]

1.2. Classification

WS is divided into four different physical types. WS type I and II are the most common forms.[7]

Type I WS: Wide space between inner canthus of eyes along with hearing loss (up to 20%).

Type II WS: No wide space between the inner canthus of the eyes but the presence of other characteristic features of WS along with hearing loss (up to 50%).

Type III WS: Also known as Klein- WS. Patients will have limb abnormalities along with other features. The rarest form of WS.[8]

Type IV WS: Also known as Shah- WS. Patients will have Hirschsprung disease with other features.[9]

1.3. Diagnostic criteria

Criteria were proposed by the Waardenburg consortium and according to this criteria, 2 major or 1 major plus 2 minor symptoms should be present to be diagnosed as a case of WS Type I.[10]

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1.4. Major criteria

1. Sensorineural hearing loss
2. Iris pigmentary abnormalities
3. Hair hypopigmentation
4. Dystopia canthorum
5. Presence of WS in first-degree relative

1.5. Minor criteria

1. Skin hypopigmentation
2. Medial eyebrow flare
3. Broad nasal root
4. Hypoplasia of ala nasi
5. Premature graying of hair (<30 years)

2. Case Report

A 7year old girl child, presented to eye OPD with a complaint of continuous watering for 4 years. The patient had no other ocular or physical complaints (as per the patient). On ocular examination, visual acuity was 6/6 in both eyes. Periorbital erythema was present due to watering along with dystopia canthi. Blue iris in left eye present (Figure 1). On direct ophthalmoscopy, a bright red fundal reflex was seen in both eyes. On indirect ophthalmoscopy, macula and optic disc were within normal limits. No choroidal and peripheral fundal pigmentary abnormalities were seen.

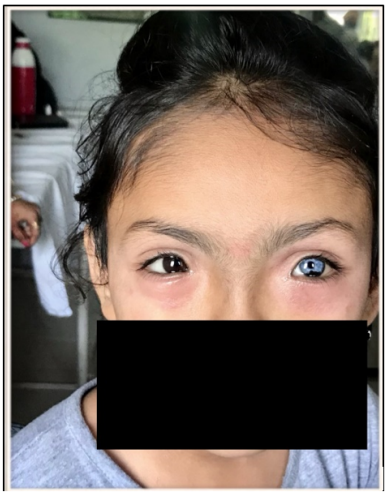

Fig. 1: Morphological features like periorbital erythema, dystopia canthi and heterochromia iridis

General physical examination revealed bilateral sensorineural hearing loss and a cochlear implant was present in the place (Figure 2). A depressed nasal bridge was also seen. As per history given by the mother she was having a white forelock of hair at birth and shed off by 2 years of age. No relevant family history was present and the younger male sibling was normal. The patient had no other complaints like any mental, limbal or gastrointestinal tract abnormalities.

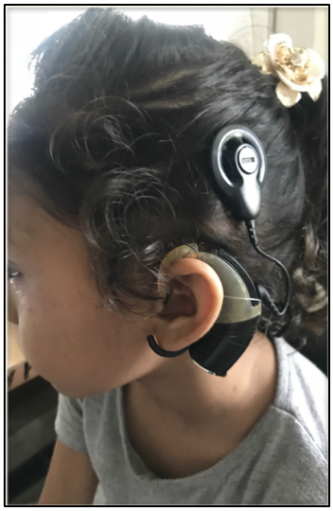

Fig. 2: Cochlear implant over left ear

As per diagnostic criteria, she was having 4 major and 1 minor feature making her a case of WS type I.

3. Discussion

WS type I, II, and IV are inherited in autosomal dominant fashion with variable penetrance and expressivity whereas WS type III is autosomal recessive.[11] Dysgenesis of the auditory-pigmentary complex leads to changes in skin, hair, and stria vascularis of cochlea giving the typical physical and morphological appearance to the patient along with SNHL.[4] These neurocristopathies sometimes also cause defects in the frontal bone, limbal muscles, and enteric ganglia as they are also derived from neural crest cells.[12]

Variable penetrance of WS may lead to different physical characteristics even among individuals having the same type of WS. Most patients present with an ocular manifestation called dystopia canthorum. Dystopia canthorum is morphologically the most penetrating sign of WS with reported penetrance even up to >95%.[12] The patient will have a typical appearance of blepharophimosis and increased inner canthal distance with laterally displaced lacrimal punctae (even up to cornea).[4,13] Waardenburg index (WI) is used to distinguish between WS type I and WS type II on basis of dystopia canthorum.[11] Different measurements required to calculate WI using caliper are inner canthal distance, interpupillary distance, and outer canthal distance.[14] Waardenburg index (WI) of >1.95 is a reliable and practical measure of dystopia canthorum.[13,15]

Ocular pigmentary changes in an anterior segment like partial or complete heterochromia iridis are reported in >25% of cases whereas hypoplastic iridis is seen in >40% of patients. Posterior segment changes like albinotic or

peripheral funds mottling are also noticed occasionally.[4] The differential diagnosis for congenital heterochromia iridis includes Benign heterochromia, WS, Piebaldism, Congenital Horner's syndrome, Sturge Weber syndrome, Neurofibromatosis type 1, Tuberous sclerosis, Hirschsprung disease, Bloch-Sulzberger syndrome, Bourneville disease, and Parry-Romberg syndrome.[16]

Bilateral SNHL is not a universal but most serious feature of WS but penetrance is seen in >65% of WS type I and >85% of WS type II cases. It is the most common type of hearing loss associated with WS. The hearing loss is typically non-progressive and may be unilateral or bilateral.[14,17]

Pigmentary defects of skin can occur in up to 50% of cases. Hypopigmented as well as hyperpigmented patches can be seen anywhere on the body like the face, trunk, and limbs. Usually, the forehead region shows hair changes like white forelock but can involve any part of the scalp. Classic white forelock is observed in >40% of cases and is the most common hair pigmentary defect associated with WS I. Premature graying (i.e < 30 years of age) of the scalp, eyebrows, cilia, or body hair is reported in >5% of cases.[4,12,18]

4. Conclusion

Currently, no definitive treatment is available for WS. The role of prenatal diagnosis and genetic counseling is also variable due to an incomplete understanding of the molecular and genetic basis of disease. Team efforts of specialist medical professionals like ophthalmologists, dermatologists, otolaryngologists, and physicians are required to manage a case of WS. Early diagnosis of SNHL, any bony abnormalities, and Hirschsprung disease is important and can significantly improve quality of life by treatment and also prevent related complications. A child presenting with blue iris and white forelock of hair should be checked for any hearing loss if not done already. Timely diagnosis of SNHL can be treated by cochlear implants and regular speech therapy later. Vocational and social training should be given as early as possible to prevent any developmental delay in these children.

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6. Conflict of Interest

None.

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