Case Report

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Waardenburg syndrome with dry eyes: A rare association

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Abstract:

Waardenburg syndrome (WS) is a rare congenital disorder primarily characterized by characteristic facial abnormalities as dystopia canthorum and synophrys; depigmentation of the hair, skin (premature graying of hair), and/or the iris of both eyes; and/or congenital deafness. Here, we report a rare case of WS with associated dry eyes. A 4-year-old female presented with blue eyes and no tear and nasal secretion production since birth. She was also deaf and dumb since birth. On examination, it was recognized as an atypical case of WS type 2 clinically, with several classical features such as white forelock, bilateral blue iris, hypopigmented fundus, smooth philtrum, bilateral profound hearing loss, and a rare association of bilateral dry eyes. The patient was given proper refractive correction, treatment of her dry eyes, and subjected to multidisciplinary approach as for the management of sensorineural hearing loss. It was a case of WS type 2 with a rare association of bilateral dry eyes.

Keywords:

Blue iris, dry eye, Waardenburg syndrome, white forelock

Introduction

Waadenburg syndrome is a rare genetic disorder, characterized by deafness along with pigmentary anomalies and defects of neural crest derived tissues. There are four recognised types of WS, which are distinguished by their physical characteristics mainly. It is usually inherited by autosomal dominant pattern but autosomal recessive pattern has also been seen. There are five major and five minor criteria of WS. Type 1 is associated with dystopia canthorum. WS type 2 has all features of type 1 but lacks dystopia canthorum of WS type 1. Types 1 and 2 are the most common types and are associated with permanent hearing loss along with other common clinical features. Type 4 is the rarest type associated with Hirsch sprung disease. Type 3, also known as Klein–WS, can be associated with incomplete closure of the roof of the mouth (cleft palate) and/or an abnormal groove in the upper lip (cleft lip) and abnormalities in the upper limb. Usually, WS does not affect the mind and patients have normal intelligence. Our case had moderategrade, aqueous deficienttype dry eye in both the eyes with WS, which is an unreported association to the best of our knowledge. The management of WS requires a multidisciplinary approach according to the involvement of different systems and the severity of disease.

Case Report

A 4-year-old female child presented to us with a chief complaint of blue eyes and no tear and nasal secretion production since birth. She was also deaf and dumb since birth. It was not associated with redness of eyes, photophobia, or blepharospasm. She was born out of nonconsanguineous marriage, after an uneventful pregnancy and by full-term normal vaginal delivery. There was no history of any drug

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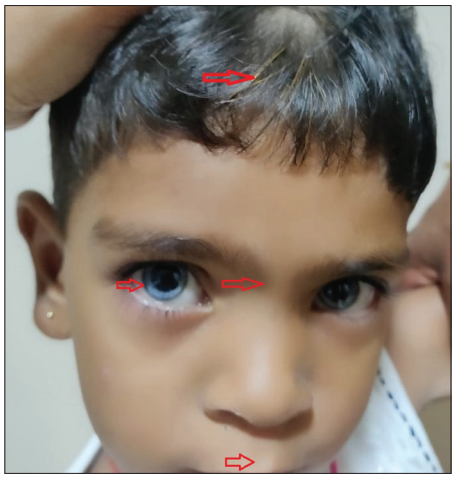

Figure 1: Bilateral blue iris, dyed white forelock, flat nasal bridge, smooth philtrum

usage, both topical and oral. Maternal history was insignificant, and the child had complete immunization as per her age. Family history was insignificant. On examination, she followed light. Retinoscopy under atropinization showed + 6 DS in the right eye and + 4 DS in the left eye. Gross and anterior-segment examinations [Figure 1] revealed white forelock which was dyed, synophrys, slightly flat nasal bridge, large eyelashes, tongue tie, smooth philtrum, and absence of adequate tear meniscus (<0.5 cm). Her interpupillary distance was 5 cm and inter innercanthal distance was 2.5 cm, signifying no telecanthus. Her Schirmer's type 1 reading was 7 mm and 6 mm wetting in the right and left eyes, respectively (moderate-grade dry eyes). There was also no dribbling of tear on crying. Blinking rate was around 15 times/min. Corneal sensation was normal, excluding any reflex hyposecretion etiology. There was no associated corneal opacity, poliosis, hypopigmented patches on the body, dry mouth, and abnormality of limbs. Both eyes had brilliantly blue iris [Figure 1]. The pupil was of normal size and normally reacting to light both direct and consensual. Fundus examination revealed both eyes with normal-sized disc, cup-disc ratio of 0.3 with peripapillary hyperpigmentation, and diffuse retinal hypopigmentation, leading to exposure of choroidal vasculature [Figure 2a and b].

A provisional diagnosis of Waardenburg syndrome (WS) type 2 was made. Complete systemic examination was undertaken. Ear, nose, and throat evaluation [Figure 3] by otoacoustic emission revealed results suggestive of abnormality up to the level of outer hair cells. Auditory steady-state response showed profound hearing loss. Brainstem-evoked response audiometry showed bilateral profound hearing loss. Impedence audiometry demonstrated bilateral A-type waves with absent reflex, and free-field audiometry showed bilateral moderate-to-severe hearing loss.

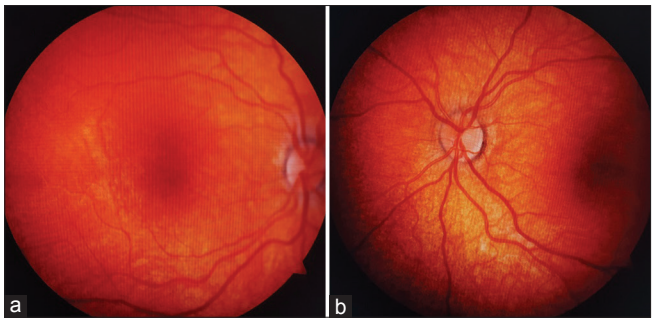

Figure 2: (a and b) Diffuse retinal hypopigmentation leading to exposure of choroidal vasculature

There was no associated megacolon or gonadal dysgenesis on ultrasonography abdomen. Magnetic resonance imaging orbit revealed no lacrimal gland dysgenesis, but there was associated vestibular and cochlear dysplasia. Based on the overall findings, a provisional diagnosis of WS type 2 was made. The patient's parents were given proper genetic counseling, and the patient was subjected to multidisciplinary management. The patient was advised diet rich in omega 3 fatty acids and Vitamin A. Proper refractive correction along with tear substitute was given and was advised usage of hearing aid.

Discussion

WS is a rare congenital disorder primarily characterized by characteristic facial abnormalities such as dystopia canthorum and synophrys; depigmentation of the hair, skin (premature graying of hair), and/or the iris of both eyes; and/or congenital deafness. WS is named after a Dutch ophthalmologist, P. J. Waardenburg. The worldwide incidence of WS is estimated at around 1/40,000. It shows no racial, ethnic, or gender predilection. It has four types and has mainly autosomal dominant inheritance, although types 2 and 4 can have autosomal recessive inheritance. Types 1 and 2 are the most common types. It is due to mutation in genes responsible of making of melanocytes. Till date, mutations in the following six different genes have been identified: PAX3 (2q36.1), MITF (3p14 p13), SNAI2 (8q11.21), SOX10 (22q13.1), EDNRB (13q22.3), and EDN3 (20q13.32).

According to the diagnostic criteria proposed by the Waardenburg consortium,[1] a person must have two major or one major plus two minor criteria to be diagnosed as WS type 1. The major criteria are sensorineural hearing loss, iris pigmentary abnormality (two eyes of different color or one iris of two colors or characteristic brilliant blue iris), hair hypopigmentation (white forelock or whitening of hairs at other sites on the body), dystopia canthorum (lateral displacement of the inner canthi), and the presence of a first-degree relative previously diagnosed

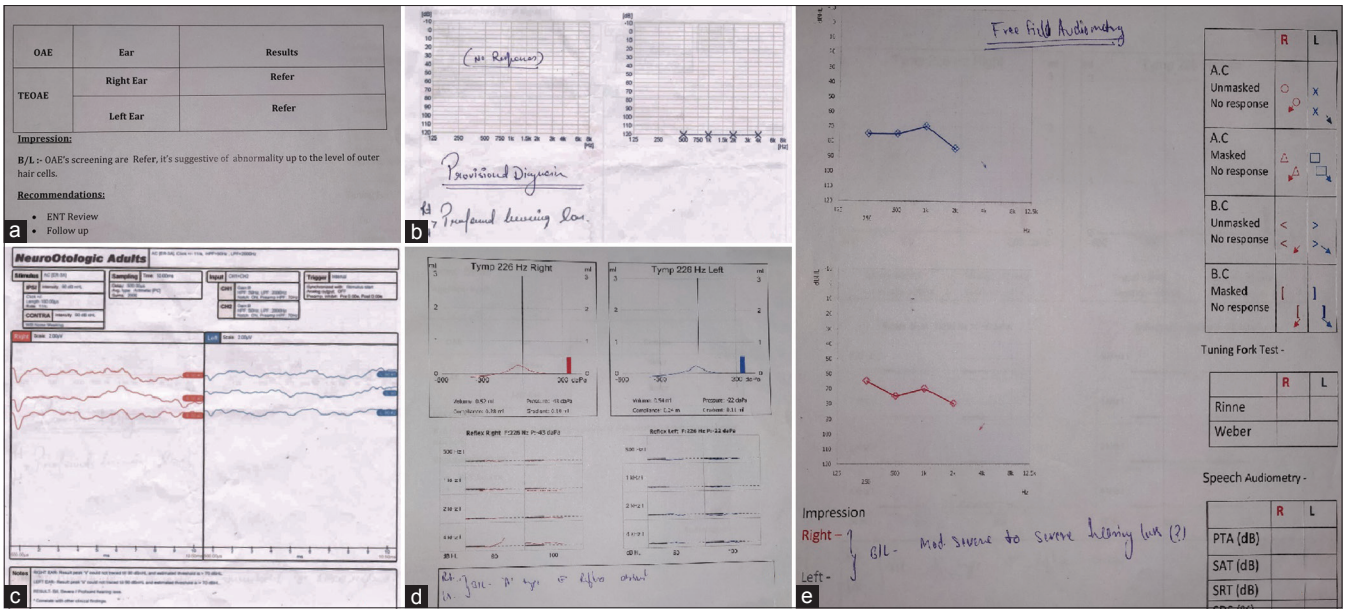

Figure 3: (a) Otoacoustic emission: results suggestive of abnormality up to the level of outer hair cells. (b) Auditory steady-state response suggesting profound hearing loss. (c) Brainstem-evoked response audiometry: bilateral profound hearing loss. (d) Impedence audiometry: bilateral A-type waves with absent reflex. (e) Free-field audiometry: bilateral moderate-to-severe hearing loss

with WS. The minor criteria are skin hypopigmentation, medial eyebrow connected (synophrys), broad nasal root, hypoplasia of nasal alae, and premature graying of hairs (before the age of 30).

Type 1 is associated with dystopia canthorum. WS type 2 has all features of type 1 but lacks dystopia canthorum of WS type 1. Types 1 and 2 are the most common types and are associated with permanent hearing loss along with other common clinical features. Type 4 is the most rare type associated with Hirschsprung disease (congenital megacolon) and is also known as Waardenburg–Shah syndrome.

Other associations are rounded nasal tip that may be slightly upturned, mild mandibular prognathism, and full lips with abnormal "smoothness" of the vertical groove of the upper lip (philtrum). Type 3, also known as Klein–WS, can be associated with incomplete closure of the roof of the mouth (cleft palate) and/or an abnormal groove in the upper lip (cleft lip) and abnormalities in the upper limb. Usually, WS does not affect the mind and patients have normal intelligence.

Dry eye syndrome in children can be associated with systemic disorders such as Sjogren's syndrome, Riley–Day syndrome, ectodermal dysplasia syndrome, hypovitaminosis-A due to congenital small bowel atresia, and graft-versus-host disease following bone marrow transplantation.[2] Congenital lacrimal gland agenesis is a rare cause of dry eye in childhood and is characterized by aplasia or hypoplasia of the principal lacrimal gland.[3,4] Our case had moderate-grade, aqueous deficient-type dry eye in both the eyes with WS, which is an unreported association to the best of our knowledge. Tear film breakup time (TBUT) could not be performed as the child was deaf and dumb and did not cooperate for these tests.

Diagnosis of dry eyes was made based on Schirmer's reading only.

The management of WS requires a multidisciplinary approach according to the involvement of different systems and the severity of disease. Folic acid supplementation in pregnancy has been recommended for women at increased risk of child with WS.[5]

In the current scenario, the major treatment options for aqueous deficient dry eye provide only symptomatic relief, and there is much to be explored for long-term sustainable options. In this regard, main strategies in pipeline are exploiting the ability of *in vivo* intrinsic regenerative capacity of the lacrimal gland and bioengineered lacrimal gland implants.

It has been shown that inflammation-induced injury stimulates the intrinsic regenerative capacity of lacrimal gland.[6]

As far as bioengineered lacrimal gland implant is considered, it is a promising modality in the treatment of aqueous deficient dry eye; however, graft rejection and donor storage[7] are some limitations.

Both the treatment strategies require in-depth understanding and knowledge of lacrimal gland development at molecular level.

These strategies can be a boon for syndromes as in our case where lacrimal gland hypoplasia is noted.[8]

Conclusion

It is a rare case of WS type 2 clinically with bilateral dry eyes, which is a rare association. Till now, to the best of our knowledge, no case has been reported of WS with dry eyes. It will add useful information in the literature of the disease and aid in the management in future.

Informed consent

Informed consent was obtained from the patient's parent.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the parent has given his consent for his child's images and other clinical information to be reported in the journal. The parent understands that his child's name and initial will not be published and due efforts will be made to conceal patient identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

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