ISSN: 2634 - 680X

Journal of Clinical Case Studies Reviews & Reports

SCIENTIFIC Research and Community

Case Report

Open Access

Rare Case of Waardenburg Syndrome WS Type 2 With Squint (Congenital Esotropia) Superior Rectus Right Eye in a 8-Year-Old Child in Pakistan

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ABSTRACT

Waardenburg syndrome (WS) is a rare autosomal dominant disorder accounting for over 2% of congenital deafness cases. It is characterized by sensorineural hearing loss, pigmentary abnormalities of the hair, skin, and eyes, and anomalies in neural crest-derived tissues. We report the first documented case in Pakistan of an 8-year-old girl with WS type 2, presenting with bilateral profound sensorineural hearing loss, a white forelock, synophrys, and broad nasal root, fulfilling clinical diagnostic criteria established by the Waardenburg Consortium. Uniquely, she also exhibited superior rectus squint causing congenital esotropia, surgically corrected at age 6, along with seizures and global developmental delay. Early referral for speech rehabilitation and specialized schooling resulted in marked improvement, allowing integration into mainstream education. This case highlights the importance of recognizing atypical features, implementing early multidisciplinary intervention, and providing genetic counseling in managing WS and related neurocristopathies.

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Received: September 02, 2025; **Accepted:** September 12, 2025; **Published:** September 18, 2025

Keywords: Waardenburg Syndrome Type 2, Sensorineural Hearing Loss, White Forelock, Superior Rectus Squint, Esotropia, Neurocristopathy, Global Developmental Delay

Introduction

Waardenburg syndrome (WS) is a genetically heterogeneous disorder, accounting for over 2% of congenital deafness cases [1-3]. It is an autosomal dominant condition with an estimated incidence of 1 in 40,000 individuals [4-8]. WS is characterized by sensorineural hearing loss, distinctive pigmentation anomalies of the skin, hair, and eyes, and various defects involving neural crest-derived tissues [1]. These auditory-pigmentary manifestations arise due to the absence of melanocytes in the skin, hair, eyes, or the stria vascularis of the cochlea [1]. Melanocytes are responsible for producing melanin, a pigment essential for normal pigmentation and inner ear function [1].

Mutations in several genes-including PAX3, MITF, SNAI2, SOX10, EDN3, and EDNRB—disrupt melanocyte development and function, resulting in the characteristic features of WS such as sensorineural hearing loss and pigmentary abnormalities [1]. Based on clinical presentation and the specific gene mutations involved, WS is classified into four types: Types I and III are linked to PAX3 mutations, Type II to MITF or SNAI2 mutations, and Type IV to mutations in SOX10, EDN3, or EDNRB [4]. Among these, Types I and II are the most prevalent [9]. Notably, a 1977 study reported a 19% incidence of convergent strabismus (esotropia) among patients with WS [10].

We present the first documented case in Pakistan of WS type 2 with the unusual finding of superior rectus involvement causing esotropia in an 8-year-old girl. This case also underscores the importance of early speech rehabilitation and timely corrective ocular surgery to improve long-term outcomes in such patients.

Case Report

An 8 year old girl presented to our hospital speech and rehabilitation department as a follow up case of Waardenburg syndrome type 2. Her past medical history includes being admitted to hospital multiple times for various medical problems At 4 1⁄2-year-old she was brought with complaints of generalized tonic clonic seizures beginning at 6 months of age. These episodes were accompanied by repeated falls and persistent global developmental delay. She achieved neck holding at 1½ years, sitting with support at 2 1⁄2 years, and by this age was only able to say a few words such as "mama," "baba,". She was born at term via spontaneous vaginal delivery after an uneventful antenatal course. Birth was complicated by a delayed cry, requiring a 2-day NICU stay. Since birth, she has had intermittent constipation. Her immunizations were complete as per schedule. Family history revealed that both her grandfather and elder brother had heterochromia iridis (change in iris color) but there was no documented hearing impairment in them. On physical examination, she had a white forelock (hypopigmented frontal hair patch), hypertrichosis of the medial eyebrows (synophrys), and a broad nasal root. Audiological testing confirmed bilateral profound sensorineural hearing loss.Due to lack of genetic testing facility for genes involved in causing various neurocutaneous syndromes in Pakistan, her diagnosis of waardenburg was based on medical history and clinical features upon examination fulfilling Waardenburg syndrome (2 major and 2 minor based on Waardenburg Consortium in 1992) type 2 criteria (absence of dystopia canthi) [5, 6]. Differential diagnoses considered included

Woolf syndrome (albinism with deafness), Fisch syndrome (early greying with congenital deafness), Hermansky-Pudlak syndrome (oculocutaneous albinism and bleeding diathesis), and Chediak-Higashi syndrome. The absence of immunodeficiency, bleeding tendencies, or diffuse albinism made these alternatives less likely. Additionally, she had a superior rectus squint causing esotropia which caused her difficulty to follow visual cues and read with visual acuity of 15/20 in right eye and 20/20 in left eye and lack of ability to focus when she was of school going age. However this was surgically corrected through strabismus surgery (6) at the age of 6 years. Below is the Pure Tone Audiogram recorded at 2 years of age figure 1

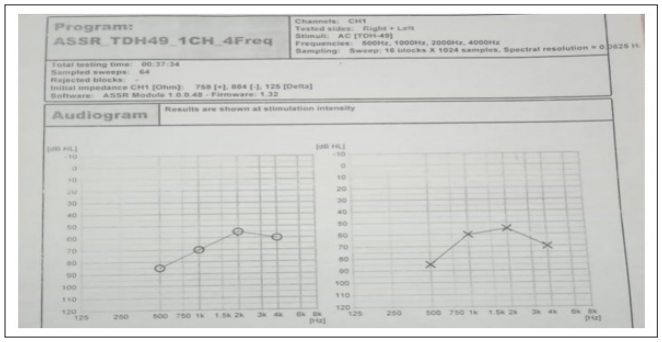

Figure 1: Pure Tone Audiogram Recorded at 2 Years of Age

Figure 2 (a): Female Child at 8 Years of Age with White Forelock and Hypertrichosis after Correction of Exotropia

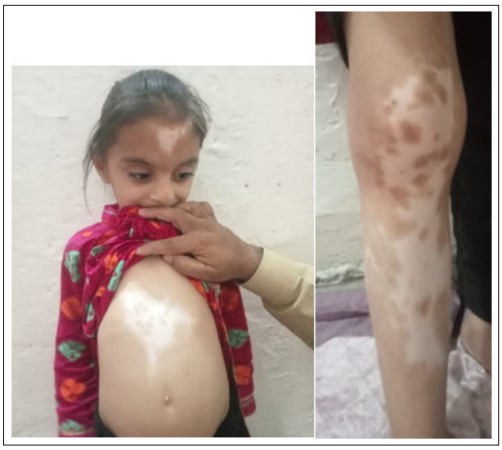

Figure 2(b, c): Hypopigmented Patches on Front of Trunk and Right Leg

The girl initially being unable to speak and hear properly was referred to speech and rehabilitation center of CMH lahore at 3 years of age where she underwent extensive speech and auditory retraining and visual training, she was also admitted in special school, but following the retraining therapy she regained most of her speech and is now admitted to a normal school. She is now able to compete children of her age in terms of mental capabilities and speech and able to score well in school examination. She regularly comes to hospital for follow up and is now in good health.

Discussion

Waardenburg syndrome is characterized by the physical absence of melanocytes affecting the skin, hair, eyes, or stria vascularis of the cochlea [2]. Because all melanocytes-except those in the retina-originate from the embryonic neural crest, Read and Newton[5] proposed that WS types I, III, and IV represent neurocristopathies, involving additional neural crest-derived tissues such as the frontal bone, limb muscles, and enteric ganglia, respectively. Alternatively, the absence of melanocytes may reflect defects specific to melanocyte development, where melanoblasts fail to migrate, differentiate properly, or survive in their final locations; some cases of WS II likely fall into this category [3]. WS has also been described within the broader group of first arch syndromes [11].

Recognizing the varied clinical presentation, the Waardenburg Consortium in 1992 established standardized diagnostic criteria that include both major and minor features. For a diagnosis of WS type I, the presence of at least two major criteria, or one major plus two minor criteria, is required [5, 6].

Major criteria

- Congenital sensorineural type of hearing loss (present from birth)
- Heterochromia iridis (either complete or segmental); iso hypochromia iridis (pale blue eyes); or defective pigmentation in fundus
- Hair pigmentation such as white forelock or loss of hair color
- Dystopia canthorum (characteristic of WS types 1 and 3)
- First-degree relative with Waardenburg syndrome

Minor criteria

- Leukoderma from birth
- Synophrys or medial eyebrow flare
- Broad or high nasal bridge (uppermost part of the nose); hypoplasia of the nostrils
- Premature graying of hair (before age 30)

Dystopia canthorum is the most consistently penetrant feature of WS, reported in 41.2% to 99% of cases [7]. Clinically, it presents as blepharophimosis with increased inner canthal distance, positioning the lacrimal puncta opposite the cornea [3, 7]. To objectively quantify this feature, Arias and Mota introduced the Waardenburg Index (WI), with a diagnostic threshold revised from >2.07 to >1.95 for improved utility [3, 7].

Hearing loss, though not universal, is common. Sensorineural hearing loss shows a penetrance of approximately 69% in WS I and 87% in WS II when excluding individuals identified solely by their hearing impairment [7, 8].

Cutaneous pigmentary changes are seen in 8.3% to 50% of patients, often presenting as piebaldism like depigmented patches on the face, trunk, or limbs, or as hyperpigmented macules [3].

Hair anomalies include a white forelock-most commonly on the forehead but sometimes elsewhere-and premature graying of the scalp, eyebrows, eyelashes, or body hair, reported in about 7% of cases [7].

Ocular findings commonly include partial or complete heterochromia iridis in 21% to 28% of patients, and hypoplastic blue irides in 14.9% to 42% [7]. The ocular fundus may appear albinotic or show peripheral pigment mottling.

At the molecular level, WS I and WS III are associated with mutations in the PAX3 gene on chromosome 2q37. The considerable phenotypic variability observed-even within families-suggests that other modifier genes influence expression [3, 7]. Read and Newton proposed that frontal bone development is most sensitive to PAX3 dosage, melanocytes to a lesser extent, and limb development the least-explaining why frontal bone defects are nearly universal in loss-of-function mutations, whereas pigmentary changes and hearing impairment vary, and limb anomalies in WS III often require homozygosity [3, 7].

MITF, mapped to 3p12–p14.1 and the human counterpart of the mouse microphthalmia (mi) gene, is implicated in WS II [12, 13]. Homozygous mutations in EDN3 or EDNRB can result in the WS IV phenotype, while heterozygous carriers typically remain unaffected or may present solely with Hirschsprung disease [3].

Conclusion

This case highlights a classic presentation of Waardenburg syndrome 2 with additional atypical features such as seizures, global developmental delay, and superior rectus strabismus. The coexistence of these findings underscores the need for a multidisciplinary approach including genetic counseling, neurodevelopmental support, ophthalmologic evaluation, and audiologic rehabilitation. Recognition of expanded phenotypic variability is essential for early diagnosis and appropriate management of WS. Our study had limitations of appropriate genetic tests availability in Pakistan in order to establish a solid association of congenital esotropia and WS, this area requires further testing and research.

Acknowledgments

The authors would like to thank the patients and their families.

Declaration of Patient Consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial Support and Sponsorship

Nil.

Conflicts of Interest

There are no conflicts of interest

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