Research Article

Waardenburg Syndrome Type 1 in 1-Year-Old Male: A Comprehensive Case Study Report

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ABSTRACT

Waardenburg syndrome, a relatively rare autosomal dominant disorder occurring in approximately 1 out of 40,000 individuals, is characterized by sensorineural deafness, skin, hair, and iris pigmentation irregularities, and various problems related to neural crest-derived tissues. This genetic condition, which constitutes over 2% of congenital deafness cases, can be caused by mutations in several genes including *EDN3, EDNRB, MITF, PAX3, SNAI2*, and *SOX10*. We present a case of a 1-year-old boy who came with the main concern of uncontrolled seizures and fever. He displayed typical features of Waardenburg syndrome, notably a distinctive white patch of hair in the center of his head along with striking blue and brown iris colors. Additionally, a white unpigmented area was observed on his right forearm. Both eyes exhibited a vivid red reflection from the back of the eye with a lack of pigmentation in the choroid. Despite having the characteristic white patch of hair, depigmented skin, and choroidal depigmentation, the young boy had normal hearing. It is noteworthy that his father had a history of premature hair graying. Medical professionals encountering a child with blue eyes and a white hair patch should promptly arrange for hearing assessment if not already conducted. Timely identification and management of hearing issues play a crucial role in the emotional and cognitive development of children affected by Waardenburg syndrome.

Key Words: Case report, Wardenburg's syndrome, Sensorineural hearing loss, Pigmentation abnormalities, Genetic disorder

Introduction

Waardenburg syndrome, initially described by Dutch ophthalmologist Petrus Johannes Waardenburg (1886–1979) in 1951, is an autosomal dominant disorder occurring at a rate of 1 in 40,000. Its characteristics include sensorineural deafness, defects in skin, hair, and iris pigmentation, as well as various neural crest-derived tissue anomalies [1, 2]. This genetically diverse condition accounts for over 2% of those born with congenital deafness [3]. These syndromes, which combine auditory and pigmentary aspects, result from the absence of melanocytes in the eyes, skin, hair, or the cochlea's stria vascularis. Waardenburg syndrome can be caused by mutations in the *EDN3, EDNRB, MITF, PAX3, SNAI2,* and *SOX10* genes. These genes play a role in the development of different cell types, including melanocytes responsible for pigment production. Melanin, the pigment these cells create, contributes to skin, hair, and eye color, and is vital for proper inner ear function. Genetic mutations disrupt melanocyte development, leading to abnormal pigmentation and hearing issues. Based on clinical features and implicated genes, Waardenburg syndrome is categorized into four types: Type 1, 2, 3, and 4 (Table 1). Types I and III stem from *PAX3* gene mutations, while type II is attributed to *MITF* and *SNAI2* mutations. Type IV arises from *SOX10, EDN3*, or *EDNRB* gene mutations [4].

We present a case of a 1-year-old male exhibiting uncontrolled seizures and fever as his main complaint, along with clinical indications aligning with Waardenburg syndrome.

Case Presentation

A 1-year-old male was brought to the hospital's emergency care due to uncontrolled seizures and fever. Comprehensive evaluation the child's history and physical appearance raised concerns, particularly related to delayed speech and language milestones. The parents observed a lack of response to auditory stimuli and limited babbling, indicating potential hearing

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impairment. Noteworthy facial features, including a white forelock, heterochromia iridium, and a broad nasal bridge, pointed towards syndromic involvement. A thorough examination revealed distinct facial attributes, such as a high nasal bridge, hypertelorism, and a prominent forehead. Heterochromia iridum was evident, with distinct iris colors (blue and brown). A striking white forelock was evident amidst the child's dark hair. No additional cutaneous pigmentation irregularities were observed. Furthermore, a depigmented white area was observable on his right forearm additionally, there was a noticeable swelling in the thyroid region of his neck. The mother reported a history of extended labour and a home birth, accompanied by a delayed cry upon birth. Despite this, the child's developmental milestones were typical. It's worth mentioning that the father had a history of his hair graying prematurely since the age of 15, although he did not experience any hearing impairment.

The patient also displayed dystopia canthorum, a feature associated with Type I Wardenburg's Syndrome, along with mild musculoskeletal abnormalities. Further evaluation excluded the presence of Hirschsprung disease.

Diagnostic evaluation

Considering the characteristic clinical indications, a preliminary diagnosis of Waardenburg Syndrome was considered. Further investigations encompassed audiological assessment (Table 1) and genetic testing (Table 2). Audiometry affirmed bilateral sensorineural hearing loss, a hallmark manifestation of Waardenburg Syndrome (Figure 1).

Genetic testing unveiled a heterozygous pathogenic variant within the *PAX3* gene, definitively establishing the diagnosis of Waardenburg Syndrome Type 1.

Given the presence of sensorineural hearing loss, bilateral hearing aids were fitted. Regular audiological monitoring sessions were scheduled to monitor auditory function and calibrate the hearing aids as necessary. Following clinical features were positive in patient reported in Table 2.

Management and treatment

Upon confirming the diagnosis, a comprehensive, multidisciplinary approach was undertaken to holistically address the patient's needs. Early intervention played a pivotal role in optimizing language acquisition and overall quality of life. Speech therapy interventions were employed to stimulate language development and enhance communicative abilities (Table 3).

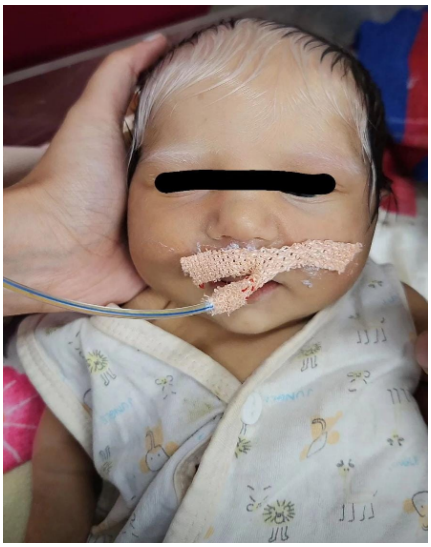

Figure 1: An image showing the white forelock of the baby

Table 1: Subtypes of Wardenburg's syndrome

Subtype	Features	Associated Genes
Type I	Pigmentation, hearing loss, dystopia canthorum	*PAX3*
Type II	Hearing loss, pigmentary disturbances	*MITF*
Type III	Hearing loss	*PAX3, MITF, SOX10*
Type IV	Hirschsprung disease, hearing loss	*EDNRB, EDN3, SOX10*

Table 2: Audiometric data

Frequency (Hz)	Right Ear (dB HL)	Left Ear (dB HL)
250	25	30
500	30	35
1000	40	45
2000	55	60
4000	70	75
8000	80	85

Table 3: Genetic testing results

Gene	Mutation	Phenotype
PAX3	Heterozygous mutation	Wardenburg's Syndrome

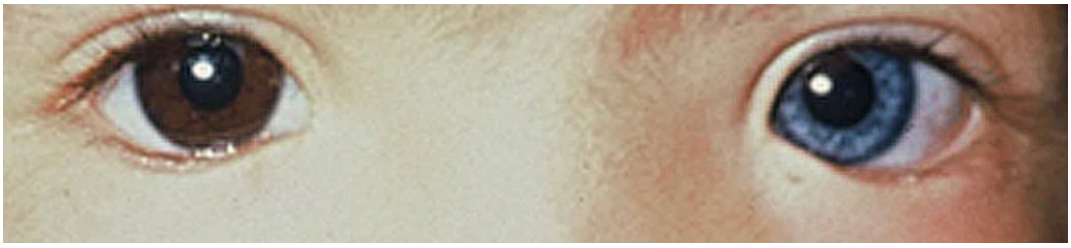

Figure 1: Pigmentation abnormalities, a hallmark of Wardenburg's Syndrome

Table 4: Subtypes of Wardenburg's syndrome

Subtype	Features	Associated Genes
Type I	Pigmentation, hearing loss, dystopia canthorum	*PAX3*
Type II	Hearing loss, pigmentary disturbances	*MITF*
Type III	Hearing loss	*PAX3, MITF, SOX10*
Type IV	Hirschsprung disease, hearing loss	*EDNRB, EDN3, SOX10*

Patient perspective

Patient parents were explained about the syndrome and the related prognosis. They wanted to seek immediate treatment but were hesitant with the diagnosis and did not follow up regularly.

Discussion

Wardenburg's Syndrome, first described by German ophthalmologist Karl Wardenburg in 1951, is a rare inherited disorder with a variable presentation and penetrance. The syndrome's diverse clinical features arise from disturbances in the migration and differentiation of neural crest cells during embryonic development, leading to anomalies in multiple systems. Our case aligns with Type I Wardenburg's syndrome, also known as Waardenburg-Shah syndrome, which encompasses pigmentary disturbances, sensorineural hearing loss, and features of Hirschsprung disease. The *PAX3* gene, located on chromosome 2, encodes a transcription factor vital for the development of neural crest-derived cells, including melanocytes and certain cranial ganglia [5].

Pigmentation abnormalities, a hallmark of Wardenburg's Syndrome, originate from the absence or reduction of melanocytes in the epidermis, hair follicles, and iris. This gives rise to the characteristic white forelock, heterochromia iridis, and depigmented skin patches seen in affected individuals. Dystopia canthorum, the lateral displacement of the inner canthi of the eyes, aids in clinical diagnosis, especially in Type I. These features, although often cosmetic, provide essential clues for early recognition and intervention (Figure 2).

Hearing loss in Wardenburg's Syndrome is typically congenital and sensorineural, as observed in our case. The underlying pathology involves the incomplete migration of Melanoblasts to the stria vascularis of the cochlea, causing disruption of potassium homeostasis and eventual hair cell degeneration. The severity of hearing impairment can vary widely, from mild to profound, and tends to worsen with age (Table 4). Early audiological assessment and intervention are crucial to mitigate the impact on speech and language development [6].

The interplay of *PAX3* mutations and other genetic factors results in the vast phenotypic spectrum of Wardenburg's Syndrome. Notably, there are genotype-phenotype correlations, such as the presence of limb anomalies in patients with certain *PAX3* mutations. Advances in molecular genetics have enabled precise identification of mutations, aiding prognostication and genetic counseling. Genetic testing in our case confirmed a heterozygous *PAX3* mutation, supporting the diagnosis of Type I Wardenburg's Syndrome [7].

Conclusion

This case underscores the importance of

recognizing and managing Wardenburg's syndrome comprehensively. Collaborative efforts among otolaryngologists, geneticists, and audiologists are critical for early diagnosis, genetic counseling, and appropriate interventions. The integration of genetic insights into clinical management enhances the quality of life for individuals with Wardenburg's syndrome. Early identification, meticulous assessment, and holistic management are paramount to meeting the unique requirements of affected individuals. Hence, timely interventions and sustained follow-up in enhancing developmental and communicative outcomes for children diagnosed with Waardenburg Syndrome. Ongoing medical support and family education will play a pivotal role in shaping a promising future for the patient as he progresses through various developmental stages.

Data Availability Statement

The data that support the findings of this article are available from the corresponding author upon reasonable request.

References

1. Waardenburg, Johannes P. "A new syndrome combining developmental anomalies of the eyelids, eyebrows and noseroot with pigmentary anomalies of the iris and head hair and with congenital deafness; Dystopia canthi medialis et punctorum lacrimalium lateroversa, hyperplasia supercilii medialis et radicis nasi, heterochromia iridum totaliis sive partialis, albinismus circumscriptus (leucismus, polioss) et surditas congenita (surdimutitas). Am. j. hum. genet. 3, 195(1951).
2. Pingault V, Ente D, Dastot-Le Moal F, et al. Review and update of mutations causing Waardenburg syndrome. Hum. mutat. 31, 391-406(2010).
3. Bondurand N, Pingault V, Goerich DE, et al. Interaction among SOX10, PAX3 and MITF, three genes altered in Waardenburg syndrome. Hum. mutat. 13, 1907-1917(2000).
4. Sánchez-Martín M, Rodríguez-García A, Pérez-Losada J, et al. SLUG (SNAI2) deletions in patients with Waardenburg disease. Hum. mol. genet. 11, 3231-3236(2002).
5. Read, Andrew P., Valerie E. Newton. Waardenburg syndrome. Journal of medical genetics.8, 656-665(1997).
6. Tekin M, Bodurtha JN, Nance WE, et al. Waardenburg syndrome type I: dental and craniofacial findings. Am J Med Genet.101, 135-139(2001) .
7. Chen H, Jiang L, Xie Z, et al. A case report of Waardenburg syndrome type IIb: Identifying novel mutations in PAX3 gene. Med. Baltim. 96, e8105 (2017).