

## Waardenburg syndrome: case report of a child and his family group in a Health Unity

*Síndrome de Waardenburg: relato de caso de criança e seu grupo familiar em uma Unidade Básica de Saúde*

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### ABSTRACT

**Objectives:** The present study aims to describe the characteristics of patients with Waardenburg syndrome, explain the pathophysiology of the syndrome in question, reaffirm the importance of interprofessional care for patients and reinforce the relevance and need for genetic counseling and the study of the language of signals. **Case Report:** A four-year-old male patient presented suspected Waardenburg syndrome in the maternity ward due to the phenotype of poliosis (frontal white streak), hypopigmentation on the face and bright blue irises. At nine months, the beginning of a hearing loss was noticed. The diagnosis was confirmed by clinical evaluation and the Brainstem Evoked Response Audiometry exam was instructed to confirm the hearing loss. After diagnosis, the presence of phenotypic characteristics indicative of Waardenburg syndrome was noted in six other family members - mother, maternal grandfather and brother, great-grandfather's cousin, two great-uncles. **Conclusion:** Early diagnosis allows adequate stimulation for hearing loss and reinforces the importance of genetic counseling and family planning, in addition to allowing the family to study sign language, aiming to improve the quality of life of patients with Waardenburg syndrome.

**Keywords:** Syndrome; Waardenburg syndrome; Pediatrics; Genetics.

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## RESUMO

**Objetivos:** O presente estudo tem por objetivo descrever as características de pacientes portadores da síndrome de Waardenburg, explicar a alteração genética da síndrome em questão, reafirmar a importância do cuidado interprofissional para com os pacientes, e reforçar a relevância e necessidade do aconselhamento genético e do estudo da linguagem de sinais. **Relato de Caso:** Paciente do sexo masculino, quatro anos, apresentou suspeita de síndrome de Waardenburg na maternidade pelo fenótipo apresentando poliose (mecha branca frontal), hipopigmentação em face e íris azuis brilhantes. Aos nove meses, foi notado início de diminuição auditiva. O diagnóstico foi confirmado mediante avaliação clínica e orientado a realização do exame *Brainstem Evoked Response Audiometry* para confirmação da perda auditiva. Após o diagnóstico, notou-se a presença de características fenotípicas indicativas da síndrome de Waardenburg em outros seis integrantes da família - mãe, avô materno e irmão, primo do bisavô, dois tios-avôs. **Conclusão:** O diagnóstico precoce permite estimulação adequada para a perda auditiva e reforça a importância do aconselhamento genético e planejamento familiar, além de permitir que a família estude a linguagem de sinais, objetivando a melhora da qualidade de vida do paciente portador da síndrome de Waardenburg.

**Palavras-chave:** Síndrome; Waardenburg; Pediatria; Genética.

## INTRODUCTION

Waardenburg syndrome (WS) is a rare disorder of neural crest cell development, which was first described in 1951 by ophthalmologist Petrus Waardenburg, who observed the following characteristics: dystopia canthorum, heterochromia of the iris and hearing loss<sup>1,2</sup>.

Currently, WS encompasses several hereditary disorders, being divided into four types - WS1, WS2 (A and B), WS3, WS4, and is responsible for about 2 to 5% of cases of congenital deafness<sup>1-10</sup>. The phenotypic manifestations of patients with Waardenburg syndrome are varied and each type (WS1, WS2, WS3 and WS4) has phenotypes that range to varying degrees<sup>11-14</sup>. In 20% of cases, the syndrome is not fully manifested, which is due to its heterogeneity and variable expression. Clinical manifestations include

hypopigmentation of the skin (which can be found on the face, torso and limbs, and can also affect the eyebrow, eyelashes and hair shaft), dystopia canthorum, hearing loss and heterochromia of the irises<sup>7,8</sup>. For diagnosis, two major criteria or one major and two minor criteria must be present, as described in Table 1<sup>2,9,10</sup>. The clinical features, then, can vary between people of the same family<sup>2,4,5</sup>.

Types 1, 2 and 3 (WS1, WS2 and WS3) have an autosomal dominant genetic profile<sup>15</sup>. Type one is characterized by mutations of the PAX3 gene located on Chromosome 2. Type 2 is subdivided into two classes, the WS2A variant is characterized by mutations in the MITF gene on chromosome 3 and WS2B related to a gene located on chromosome 1. Type three (WS3) comprises patients with a deletion on chromosome 2. Several genes are found in this region, including the PAX3 gene (which participates in the

**Table 1.** Major and Minor Criteria for Waardenburg Syndrome - adapted from Nasser et al. (2012)<sup>25</sup>.

MAJOR CRITERIA	MINOR CRITERIA
Neurosensory hearing loss	Skin hypopigmentation
Dystopia canthorum	Confluence of eyebrows
Changes in iris pigmentation	Enlarged nose base
Poliosis before age 30	Nasal wing hypoplasia

Legend: This table presents the majors and minors for the diagnosis of Waardenburg syndrome.

regulation of other genes that play a role in the production of melanocytes). Type 4 (WS4) encompasses mutations in the EDNRB, EDN3 and SOX10 genes on chromosomes 13, 20 and 22 respectively. The cases involving mutations in the EDNRB and EDN3 genes have an autosomal recessive character, while those involving the SOX10 gene have an autosomal dominant profile<sup>6,12-14</sup>.

In SW1 type, dystopia canthorum is seen in 99% of those affected by this mutation. Some type of pigmentary disorder is almost always found, which may be hypopigmentation of the skin, hair and/or irises. Contrary to what occurs in albinism, where there is generalized hypopigmentation in most cases, in WS the hypopigmentation is presented in fragments. Poliosis (frontal white streak) is found in 70% of patients with type one of this disorder. The eyelashes and body hair may also show hypopigmentation. Iris heterochromia can be complete (25% of patients) or partial (5%). Hearing loss is present in 60% of individuals with WS1, and 80% are bilateral<sup>1,3,12,13,16-18</sup>. In the cases of WS2, the main phenotypic difference in relation to WS1 is the absence of dystopia canthorum. Hearing loss and iris heterochromia are common in these cases - the incidences are, respectively, 85%, and poliosis occurs in incidences of 15% to 20% in this type. In WS3 types, abnormalities in the osteoskeletal system can be found, in addition to the other symptoms common to other types. In the SW4 type, the patient rarely has hearing loss and the presence of dystopia canthorum<sup>1,3,16-18</sup>.

## METHODS

The information used to create the report was obtained through interviews with the patient's legal guardian, in addition to an evaluation of the medical record, records of diagnostic methods to which the patient was submitted and a review of the literature on the subject. The ethical records used in the reporting were: CEP (CAAE 60575722.2.0000.0197); TCLE and Image Term.

## CASE REPORT

Patient, currently four years old, male, presented suspicion of Waardenburg syndrome in the maternity ward, soon after birth, due to the expression of suggestive phenotypic characteristics: poliosis (frontal white streak) and depigmentation on the face. During pregnancy, the mother denies complications, being classified as usual risk prenatal care. After birth, the patient started follow-up at the Basic Health Unit in his city and was referred for evaluation by a geneticist. For investigation, the G-band karyotype test was initially performed, with normal results (46, XY). At nine months of age, low hearing acuity was noted by family members.

The syndromic diagnosis was confirmed by a medical geneticist at a center specializing in genetic syndromes, at eleven months of age, through clinical evaluation, guidance was given to perform the Brainstem Evoked Response

Audiometry (BERA) exam to confirm hearing loss, which was performed at two years of age, demonstrating severe bilateral deafness. The patient currently has: dystopia canthorum, bright blue irises, hearing loss, poliosis, abnormal skin pigmentation on the hands, wide nasal root and thick eyebrows, as shown in Figure 1.



**Figure 1.** Patient cited in the case report, carrier of Waardenburg syndrome, presenting the following criteria: poliosis, bright blue irises and confluence of the eyebrows.

After the diagnosis of the aforementioned patient, the presence of phenotypic characteristics indicative of Waardenburg syndrome was noted in three other family members – the maternal grandfather manifests bright blue irises, poliosis, and abnormal skin pigmentation on the hands and feet; the mother has poliosis (frontal white streak), dystopia canthorum and wide nasal root; and the sibling has only complete heterochromia (one brown and one bright blue iris). Despite these characteristics, the syndromic diagnosis was never considered by the family members, being suspected after the birth of the reported patient.

Currently, the patient frequents pediatrics follow-ups at the Basic Health Unit, attends a regular school without a mediator, and undergoes specialized follow-ups with an otorhinolaryngologist and speech therapist at an institution dedicated to people with hearing impairment, where he has classes in Brazilian Sign Language (LIBRAS), in addition to education also for his family members.

## DISCUSSION

In this case, the following characteristics were found in the patient: dystopia canthorum, bright blue irises, hearing loss, poliosis, abnormal skin pigmentation on the hands, wide nasal root, and thick eyebrows; according to studies carried out in the literature, we classified him as WS1.

The syndromic diagnosis, in turn, can be made clinically and/or by genetic tests. The clinical diagnosis is based on the association of phenotypic characteristics of the syndrome presented by the patient<sup>19</sup>. In genetic tests, a comprehensive analysis of the genes involved in the syndrome is provided through next-generation sequencing that allows an understanding of all relevant genetic aspects involved<sup>19</sup>. The patient, due to financial and local limitations, does not have

the genetic test so far and, therefore, because he has a classic phenotype of the syndrome, he received his diagnosis only clinically.

Also, when analyzing the pedigree chart of the present family (Figure 2), it was noted that the first manifestation of the syndrome was observed three generations ago. The maternal grandfather manifests bright blue irises, poliosis, and abnormal skin pigmentation on the hands and feet; the mother has dystopia canthorum, poliosis and a wide nasal root, and the brother has only complete heterochromia (one brown iris and the other bright blue). According to the mother's reports, two of the maternal grandfather's brothers also have complete heterochromia of the irises, as seen in Figure 2.

Deafness is a common disability in type 1 Waardenburg syndrome that negatively affects many aspects of an individual's life. Hearing deprivation can impair quality of life as it limits access to spoken communication (critical for developing social connections) and can lead to delayed speech development and contribute to a higher risk of cognitive decline<sup>20,21</sup>. Even with a high prevalence, hearing loss is neglected and is often undiagnosed and untreated. Data shows that only a third of people with reported deafness have had their hearing tested<sup>20,21</sup>. The management of people with hearing impairment should consist of a multidisciplinary approach, including access to hearing aids, screening programs, and learning Brazilian Sign Language (LIBRAS)<sup>20,21</sup>. Cochlear implants may also be a treatment choice for sensory deafness by implanting small electronic

devices into the cochlea that help patients with severe hearing loss<sup>22</sup>.

Regular follow-up with a geneticist should also be considered for the reported case, both for the patient and for their family members. Genetic counseling is a tool that aims to inform the patient and/or their family members about the possibility of transmitting abnormal genetic characteristics to their descendants<sup>23</sup>. Thus, through information, patients are empowered to make decisions in a conscious and responsible way, given guidance on the risk that the offspring manifest the disease or become an asymptomatic carrier<sup>23</sup>.

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## CONCLUSION

It is through language that children are situated in the world, being able to develop through access to knowledge and interpersonal relationships subsidized through the communicative process. These individuals have the right to participate in society and for this to occur, it is necessary to promote the integration of sign language in all possible scenarios<sup>24</sup>.

In the school context, for the effective inclusion of these children with hearing loss, daily multi-professional commitment and commitment becomes necessary, with the objective of optimizing learning and connecting the hearing-impaired patients to their classmates. Education professionals need to enter the entire context of sign language, understand the perspectives of inclusive education, and expand, beyond the school environment, actions for the family environment and in other social spaces<sup>24</sup>.

**Figure 2.** This family pedigree shows the onset of the syndrome in the third generation of the reported patient. In this third generation, one of the carriers of the syndrome had poliosis, bright blue irises and hypopigmentation of the skin; and two other family members had complete heterochromia.

In the case of the aforementioned patient, genetic counseling will be extremely valuable, as it will enable a more conscious choice in adult life, which was not possible in previous generations of his family, due to the lack of suspicion and diagnosis of WS<sup>25</sup>.

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## AUTHORS' CONTRIBUTION

We describe contributions to the papers using the taxonomy (CRediT) provided below:

*Conceptualization, Investigation, Methodology, Visualization & Writing – review & editing:* Lais Michelini Gabanella, Milena da Rosa Adami, Natália Botelho Libonati e Flávia Linhares Martins. *Project administration, Supervision & Writing – original draft:* Lais Michelini Gabanella, Milena da Rosa Adami, Natália Botelho Libonati e Flávia Linhares Martins. *Validation & Software:* Lais Michelini Gabanella, Milena da Rosa Adami e Natália Botelho Libonati. *Data curation & Formal Analysis:* Flávia Linhares Martins.

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