

Waardenburg syndrome Type I with dental anomaly: Case report and literature review

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ABSTRACT

Introduction: Waardenburg syndrome (WS) is a disorder of neural crest cell migration. WS was initially described as a genetic disorder with an autosomal dominant pattern of inheritance, associated with depigmentation abnormalities and sensorineural hearing loss. However, recently WS is known to be a clinically and genetically heterogeneous disorder with characteristic clinical features that include sensorineural hearing loss (SNHL), heterochromia iridis and pigmentary abnormalities of hair and skin (1). **Case Report:** A case of 16-year-old female showing the characteristic features of WS but no familial history of WS was reported. **Conclusion:** The presented features are characteristic features of Waardenburg syndrome with dental abnormalities associated with WS but with no familial history for WS proving the heterogeneity in the mode of inheritance and the clinical features of this syndrome. In this case an orthodontic treatment was planned for the patient as well as referring her for an ophthalmologist and hearing specialist.

Keywords: Auditory pigmentary syndromes, PAX3 gene mutation, Waardenburg syndrome

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INTRODUCTION

Waardenburg syndrome (WS) is a disorder of neural crest cell migration [1] described in 1951 by a Dutch ophthalmologist named Petrus Johannes Waardenburg. Prevalence of WS is estimated to be 1 in 42,000 and it accounts for approximately 2–5% of congenital hearing loss population.

The characteristic clinical features include sensorineural hearing loss (SNHL), heterochromia iridis and pigmentary abnormalities of hair and skin.

To confirm WS diagnosis, two major or one major plus two minor criteria have to be present. A first criterion is sensorineural hearing loss, which result from abnormalities or absence of the organ of Corti and is usually nonprogressive, varying from slight to profound. In most of the cases of WS bilateral ear affection occurs while in rare cases it was seen unilateral [2].

Other major criteria of WS include, iris pigmentary abnormalities which are in the form of iris bicolor or characteristic brilliant blue iris, hair hypopigmentation (white forelock or white hairs at other sites on the body), a midfacial alteration called dystopia canthorum which is lateral displacement of the inner eye corners [3, 4], recently diagnosed by the Waardenburg (W) index which is a biometric index based on interpupillary, inner canthi, and outer canthal distances: when the W index is larger than 1.95. It is considered positive for dystopia canthorum,

in addition to a first-degree relative diagnosed with WS [2].

While the minor criteria of WS will present skin hypopigmentation in the form of congenital leukoderma or white skin patches, medial eyebrow flare (synophrys), broad nasal root, hypoplasia alae nasi, and premature graying of the hair (before the age of 30) [3].

Waardenburg syndrome (WS) is classified into four types WS1, WS2, WS3 and WS4 depending on the additional symptoms present. Type I is the classic form of WS with dystopia canthorum, whereas type II is characterized by the presence of skin hypopigmentation and deafness without dystopia canthorum. Type III is similar to Type 1 WS with additional abnormalities of the upper limbs, and Type IV is characterized by the presence of Hirschsprung disease together with the WS which may be fatal [5].

CASE REPORT

A medically fit 16-year-old female patient, attended to the Faculty of Dentistry, Cairo University for tooth extraction. The facial features of the patient drawn our attention to take a detailed history along with examination, she was presenting with bilateral brilliant blue iridis (Figure 1), dystopia canthorum bilateral congenital sensorineural hearing loss (Figure 2), broad nasal root (Figure 3), hypoplastic alae of the nose, areas of skin hypopigmentation and hyperpigmentation on her hands and feet (Figure 4). The oral examination showed minimal interdental spacing in the upper jaw and hypodontia, in the form of missing upper lateral together with minimal enamel defects (Figure 5), the case required orthodontic and/or prosthodontic treatment in the future. Careful medical history showed that the patient did not have any upper limbs defect, cranial skeletal abnormalities, or intestinal disorders.

The syndrome commonly involve first-degree relative however for this patient there was no family history of the syndrome. A written informed consent was obtained from the patient's father, including use of the data and the photos for research and teaching purposes. Upon history taking the patient's father mention that his daughter condition was diagnosed in different hospital at the first year of her life after discovering the deafness. The hearing loss was discovered at the age of seven months, then the cochlear implantation of her right ear was done at 1 1/2 year of age. Second cochlear implantation for left ear was performed at the age of thirteen. He also added that his daughter is studying in high school level with mainstreaming teaching techniques. The patient experienced normal puberty process without any problems. The patient did not have any upper limbs defect, joints problems, cranial skeletal abnormalities, or intestinal disorders. All clinical features go in favor of WS. Unfortunately, we could not have done genetic counseling previously due to financial constraints.



Figure 1: Bilateral brilliant blue iridis.

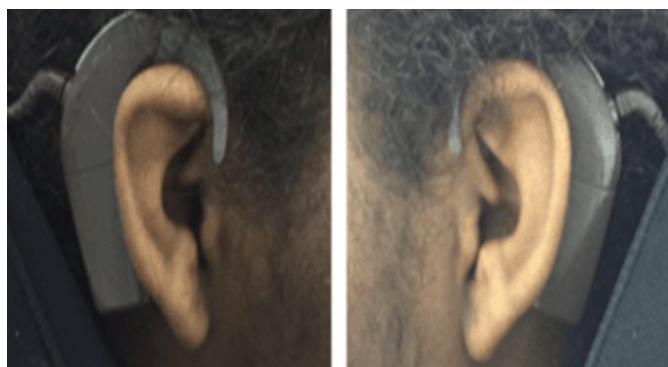


Figure 2: Bilateral hearing loss and the patient is using hearing aids bilaterally. Note her white and gray hair at age of 16.

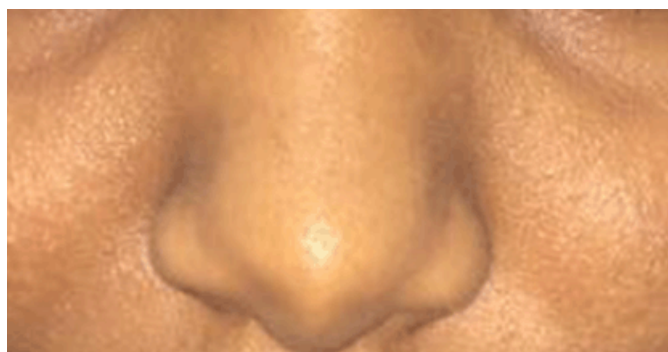


Figure 3: Broad nasal root.



Figure 4: Skin hypopigmentation and hyperpigmentation in both arms.



Figure 5: (A) Minimal teeth spacing and localized enamel hypoplasia. (B) Note the missing lateral in upper left side.

DISCUSSION

Waardenburg syndrome (WS) is a rare heterogeneous inherited disorder of the neural crest cells (NCC) that causes abnormalities in NCC-derived melanocytes, leading to pigment abnormalities and sensorineural hearing loss.

The main features of WS include sensorineural hearing loss, a white forelock, pigmentary disturbance of the iris, dystopia canthorum (lateral displacement of the inner eye corners), and first-degree relatives diagnosed with WS, together with additional features as congenitally hypopigmentation of the skin, medial eyebrow flare (synophrys), hypoplastic alae nasi, prominent broad nasal root, and early graying of hair before the age of 30 [2].

Read and Newton [6] in 1997 identified four types of WS according to the additional symptoms present. In their classification, Type 1 and Type 2 have similar features, but are distinguished by telecanthus, which is present only in Type 1. Upper limb defects are found in Type 3, while Type 4 is associated with Hirschsprung disease [7].

Choi et al. [7]; 2018, reported a Waardenburg Type 1 case in a Korean patient in which a confirmed diagnosis was reached through detection of a novel PAX3 mutation at 2q35 (c.91–95 ACTCC deletion). They were first to report additional symptoms associated with WS1 type which is presence of both Branch Retinal Vein Occlusion (BRVO) and Branch Retinal Artery Occlusion (BRAO) in the eye contralateral to the depigmented left eye, in contrast to the present case in which the patient's eyes were of brilliant blue iridis bilaterally [7].

Bandyopadhyay and co-workers in 1999, reported the oral manifestations associated with WS, they only reported dental agenesis of the lower lateral incisors in patients affected by this disorder [5].

Later studies added other oral manifestations for WS as cleft lip and high arched or cleft palate, tooth enamel malformations and fissured tongue. The jaw malformations and mandibular prognathism have been included as part of the clinical spectrum of the oral manifestations of patients affected by the syndrome [5].

The prevalence of dental agenesis vary according to the class of the tooth, with the permanent dentition being more affected than deciduous dentition. The prevalence of multiple dental agenesis (the absence of four or more teeth, other than the third molars) is estimated to be

approximately 0.25% of the population. While in other studies involving the Caucasian population the second premolar and lateral incisor were the most commonly missing teeth [5].

In the present case, missing upper left lateral incisor is present with localized enamel hypoplasia. This is in accordance to Sólía-Nasser et al. [5]; 2016 who reported that a Brazilian family were affected by WS Type 1 and showed that the majority of missing teeth were upper lateral incisors (12.19%) which was even more common than missing third molar in their study, followed by lower lateral incisors, lower central incisors, upper and lower second premolars, second molars and third molars, each with a frequency of 9.75%. Together with very uncommon dental abnormalities associated with the syndrome as, taurodontism and conical teeth [5].

Diagnosis of WS is based on the recognition of the clinical picture and is usually confirmed by identification of a mutation in one of the disease-causing genes. WS1 is caused by heterozygous variants in PAX3 (encoding the paired box 3 transcription factor), while in WS3, PAX3 mutations occur in a heterozygous as well as biallelic variants. WS2 is caused mainly by heterozygous variants in MITF (microphthalmia-associated transcription factor), SOX10 (Sry box10 transcription factor) and SNAI2 (snail homolog 2). For WS4, a homozygous and less frequently heterozygous variants in EDNRB (endothelin receptor type B) and EDN3 (endothelin 3) occur [7, 8].

As stated above PAX3 mutations are involved in WS1 and WS3 and in some cases in WS2 and 4, makes it a confirmatory tool for WS diagnosis. The PAX3 gene encodes a member of the PAX family of transcription factors that is characterized by a highly conserved paired box motif. The PAX3 protein is a transcription factor consisting of an N-terminal DNA binding domain and a C-terminal transcriptional activation domain. This protein has been implicated in the development of the ear, eye, striated muscles and face. PAX3 is also strongly expressed during tooth development, makes it responsible for most of the major criteria of this disorder [4].

Heterozygous mutations in the PAX3 gene are observed in nearly 80% of WS1 cases, whereas partial or total deletion of PAX3 and contiguous genes are often observed in WS3 cases. Approximately 100 sequence changes in the PAX3 gene have been reported in this disorder, and very few of these changes are recurrent. These reported sequence changes include missense mutations (38%), small deletions (20%), nonsense mutations (15%), gross deletion (11%), splicing mutations (8%), and small insertions (8%). The majority of these PAX3 mutations are localized mostly in exons 2 [4]. All these types of mutations are the cause that WS is now known to consist of a group of genetically heterogeneous subtypes and not all cases are inherited as an autosomal dominant manner.

In a recent study Choi et al. [7]; 2018 identified a novel PAX3 mutation (c.91–95 ACTCC deletion causing p.Thr31fs) in exon 2, which has not been reported

previously. The mutation was predicted to be highly deleterious for PAX3, adding to the literature a new PAX3 mutation involved in Waardenburg syndrome [6].

CONCLUSION

In the future, more researches with larger number of cases are required for better understanding of the mechanisms involved in the clinical manifestations of this rare syndrome and other gene mutations associated with it.

REFERENCES

1. Somashekar PH, Girisha KM, Nampoothiri S, et al. Locus and allelic heterogeneity and phenotypic variability in Waardenburg syndrome. *Clin Genet* 2018.
2. Haj Kassem L, Ahmado MF, Sheikh Alganameh M. A rare case of seven siblings with Waardenburg syndrome: A case report. *J Med Case Rep* 2018;12(1):192.
3. Dipak NK, Parab S, Nage A, Kumar A. Association of Hirschsprung disease with Waardenburg syndrome and role of gene studies: A review of 2 cases. *Indian J Child Health* 2018;5(3):216–9.
4. Boudjadi S, Chatterjee B, Sun W, Vemu P, Barr FG. The expression and function of PAX3 in development and disease. *Gene* 2018;666:145–57.
5. Luciano Sólía-Nasser L, de Aquino SN, Paranaíba LM, et al. Waardenburg syndrome type I: Dental phenotypes and genetic analysis of an extended family. *Med Oral Patol Oral Cir Bucal* 2016;21(3):e321–7.
6. Read AP, Newton VE. Waardenburg syndrome. *J Med Genet* 1997;34(8):656–65.
7. Choi EY, Choi W, Lee CS. A novel PAX3 mutation in a Korean patient with Waardenburg syndrome type 1 and unilateral branch retinal vein and artery occlusion: A case report. *BMC Ophthalmol* 2018;18(1):266.
8. Pingault V, Ente D, Dastot-Le Moal F, Goossens M, Marlin S, Bondurand N. Review and update of mutations causing Waardenburg syndrome. *Hum Mutat* 2010;31(4):391–406.

Author Contributions

Mervet M. Moussa – Substantial contributions to conception and design, Analysis and interpretation of data, Acquisition of data, Revising it critically for important intellectual content, Final approval of the version to be published

Reham S. Hamed – Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor of Submission

The corresponding author is the guarantor of submission.

Source of Support

None.

Consent Statement

Written informed consent was obtained from the patient for publication of this case report.

Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.

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