

Waardenburg syndrome type 2: an orthodontic perspective

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Abstract

Waardenburg syndrome is a rare form of neurocristopathy. It is a disorder in the development of neural crest cells, caused by an altered cellular migration during the embryonic phase. That alteration causes an association of different abnormalities such as pigmentary disturbances of the hair, iris, skin, stria vascularis of the cochlea, dystopia canthorum and sensorineural hearing loss. We report a case of a 14-year-old Romanian male, with a family history of Waardenburg syndrome (mother) and Usher syndrome (father – congenitally sensorineural hearing loss and retinal degeneration). The case particularities are: the correlation between malocclusion and Waardenburg syndrome due to hypoplastic alae nasi and also factors that produced hearing loss, which could be Waardenburg syndrome, Usher syndrome or the presence of the connexin 26 (W24X) gene mutation.

Keywords: Waardenburg syndrome type 2, white forelock, brilliant blue irides, sensorineural hearing loss, malocclusion.

Introduction

Hearing loss can occur in a wide genetic array (over 400). Inherited hearing loss as an autosomal dominant trait is most commonly found in the Waardenburg syndrome (WS). Apart from hearing loss of various degrees, depigmentary abnormalities of the hair, eyes and skin are associated with this syndrome [1]. This syndrome is determined by the absence of melanocytes from the eyes, hair and skin [2].

The incidence of WS is estimated at 2/100 000 worldwide [3], 1/42 000 in the Netherlands and 1/20 000 in Kenya and 3% in hearing impaired special schools [4].

Diagnostic criteria for WS have been proposed by the *Waardenburg Consortium*, with five major and five minor diagnostic criteria being established. Major criteria include: sensorineural hearing loss, white forelock, pigmentary disturbance of the iris (complete heterochromia irides – two eyes of different color, usually brown and blue; partial or segmental heterochromia; very pale or brilliantly blue eyes), dystopia canthorum (lateral displacement of the inner eye corners), and first degree relatives diagnosed with WS. Minor criteria include: 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 years). The clinical diagnosis of WS requires at least two major criteria or one major and two minor criteria [5, 6].

Four distinct types of Waardenburg syndrome have been described, depending on the presence of other abnormalities. Types 1 and 2 can be clinically distinguished only by dystopia canthorum ($W_{index} > 1.95$), which is characteristic of WS type 1 and absent in WS type 2 [1]. Type 3 has the same symptoms as type 1 with musculoskeletal limb abnormalities. Type 4 is called Shah–Waardenburg syndrome with only a few cases of it being reported in

literature. It is associated with Hirschsprung's disease, its most defining feature being the aganglionic megacolon [7].

We describe the case of a boy diagnosed with WS type 2, in a Romanian family with a history of WS, presenting orthodontic pathology due to the hypoplastic alae nasi. Pathophysiological states, like hypoplastic alae nasi may collapse the upper airway, making nasal breathing difficult for the patient [8], thus partially substituting it with oral breathing. Mouth breathing creates an imbalance in the forces exerted by lips, cheeks and tongue, thus leading to morphological changes in the craniofacial and dental complex [9].

Our case particularities are malocclusion and deafness, which could be polyetiological: syndromic deafness (WS or Usher syndrome), and non-syndromic deafness that may be caused by the connexin 26 (W24X) gene mutation.

Case report

During a dental check up of students from a boarding school for the hearing impaired, a 14-year-old boy with congenital sensorineural bilateral hearing loss, with a white forelock and bright blue eyes was incidentally spotted.

A written informed consent was obtained from the patient's parents, including lawful use of any pictures or images of the boy. All principles and ethical guidelines for medical research on human subjects were considered during this study.

History

The proband is the second child of non-consanguineous deaf parents. Family history revealed that the patient's mother presents suggestive features of WS (sensorineural congenital hearing loss, white forelock, brilliant blue eyes, hypoplastic alae nasi and synophrys). His elder brother

presents characteristic features of WS, such as: first degree relatives with WS-mother, premature graying of the hair before the age of 30 years, synophrys, hypoplastic alae nasi. The elder brother is a hearing person with brown eyes. Our patient's father was diagnosed with Usher syndrome (sensorineural congenital hearing loss and retinal degeneration with serious visual disorders). One of the patient's cousins from the father's side of the family was also diagnosed with sensorineural hearing loss (SNHL) and retinal degeneration.

The patient was diagnosed with hearing loss in the first year of life (lack of response to auditory stimuli). He was institutionalized from the age of three years in a Hearing and Speech Rehabilitation Center in Cluj-Napoca, Romania. Bilateral auditory prosthesis with a hearing amplifier were applied at the age of three years. The patient is well versed with gestural sign language and lip reading.

Clinical examination

Clinical evaluation was performed by an orthodontics specialist and a dentoalveolar surgery intern, under hygienic conditions (medical scrub suits, caps, latex gloves and masks), in the presence of ambient light, using a dental mirror, cheeks retractor and a dental probe, which had been previously sterilized in autoclave conditions at 135⁰C.

Extra-oral examination

On the frontal left side, a white forelock of hypopigmented hair was noted. The characteristic disturbance of iris pigmentation with brilliant blue irides was observed in our patient (Figure 1). He has synophrys-confluent eyebrows, hypoplastic alae nasi, narrow nostrils and broad nasal root.

From the frontal aspect, the patient has a narrow facial appearance, with a slight mandibular asymmetry to the left (Figure 1). He has a flattened profile with a short upper lip, a thick lower lip and lack of philtrum (Figure 2).



Figure 1 – Frontal aspect of the patient with a white forelock of hair, brilliant blue irides, synophrys, broad nasal root and narrow nostrils.



Figure 2 – Side aspect of the patient with a flat profile, short upper lip, thick lower lip.

Intra-oral examination

Dentally, the patient showed a Class II division 1 malocclusion, with proclined upper incisors and an increased overjet. The patient's canine relationship was Class I on the right side and Class II with one cuspid on

the left side. Cross-bite was observed on the upper second left premolar, upper second left molar and edge to edge second right premolar (Figures 3 and 4). Upper and lower midlines were not coincident; the lower midline was shifted 4 mm to the left (Figure 5). The facial appearance was reflected in the maxillary arch form, which was assessed as narrow and ovoid with a narrow maxilla and high arched palate (Figure 6). Several decays have been observed on the upper right lateral incisor, premolars and molars with no restorations. Upper premolar rotations were also noted.



Figure 3 – Intraoral, the Class I right canine relationship.



Figure 4 – Intraoral, the left canine was Class II with a cuspid and cross bite on second upper premolar and second upper molar.



Figure 5 – Frontal occlusion with the lower midline shifted 4 mm to the left.



Figure 6 – Maxillary dental arch with narrow maxilla, ovoid arch form and high arched palate.

The patient's deleterious oral habit was determined to be mouth breathing, which was detected using the mirror test. A two-sided mirror was placed under the patient's nostrils during exhale with formation of vapors being observed on the lower part of the mirror, thus indicating mouth breathing [10].

Multidisciplinary examinations

Otolaryngologist-conventional audiological examination revealed sensorineural profound bilateral hearing loss as shown in the audiogram in Figure 7.

Neuropsychiatric examination revealed congenital nystagmus and attention deficit hyperactivity disorder (ADHD) currently under treatment with Strattera.

Ophthalmological examination demonstrated retinal degeneration. Fundus examination revealed that both eyes had a grayer papilla, with vascular inversion and thin hypopigmented peripheral and peripapillary retina. Pigmentation around the macula was normal. The case is under further observation.

Brilliant blue irides with the absence of dystopia canthorum ($W_{index} < 1.95$) were also detected during the examination.

Dermatological, orthopedic and gastroenterological examinations showed normal functions and aspects.

Laboratory investigations (CBC – complete blood

count, Ca, P, Mg, alkaline phosphatase, glucose, SGOT – serum glutamic oxaloacetic transaminase, SGPT – serum glutamic pyruvic transaminase, urea, creatinine) were within normal limits.

Karyotype determination was not deemed necessary because the patient’s phenotype did not dispute the numerical chromosomal abnormalities or molecular structure. Molecular analysis of the case highlighted the connexin 26 (W24X) gene mutation.

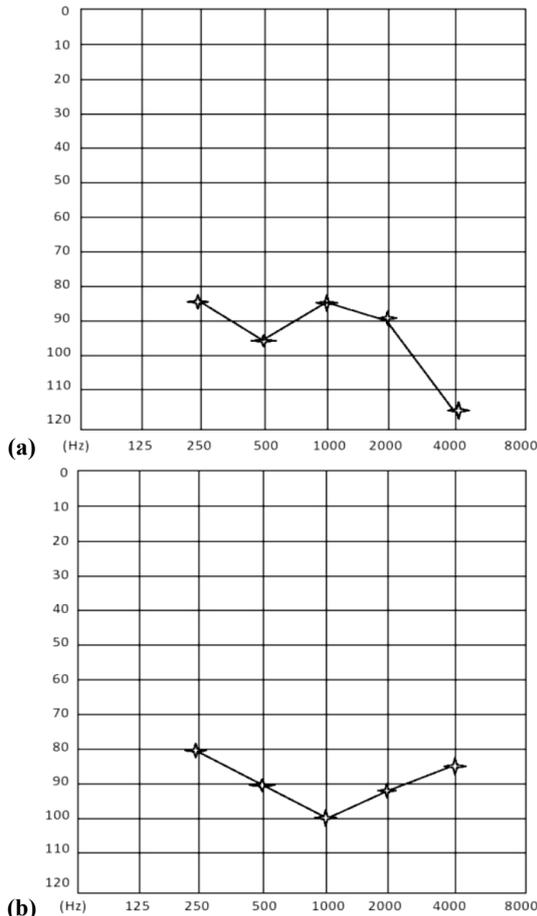


Figure 7 – Audiogram of left (a) and right (b) ear.

Discussion

WS is characterized by deafness in association with pigmentary anomalies and various defects of neural crest derived tissues [6]. Worldwide distribution of this disease can be observed, without preference for race or gender.

According to the diagnostic criteria proposed by the *Waardenburg Consortium*, a person diagnosed with WS must present two major criteria or one major plus two minor criteria [5]. Our case has all four major criteria: SNHL, white forelock, abnormal pigmentation of the iris (brilliantly blue eyes), first degree relatives diagnosed with WS (mother) and three minor criteria: synophrys, hypoplastic alae nasi and broad nasal root.

Our patient suffers from congenital deafness, which may be polyetiological: WS, Usher syndrome or the mutation of the connexin 26 gene.

SNHL in WS can be explained by the lack of the melanocyte-derived intermediate cells of the stria vascularis found in the cochlea. This absence induces endolymphatic collapse, culminating with the atrophy of Corti’s

organ, a process that is called cochleosaccular degeneration [11]. Hearing loss in WS has a congenital, sensorineural character and is usually non-progressive, varying from slight to profound. It may be unilateral or bilateral [12]. Studies performed by Müllner-Eidenböck *et al.* and Read & Newton [13, 14] showed that WS type 2 cases more often presented a bilateral aspect with severe deafness [13, 14]. WS is reported by Demirci *et al.* [15] to account for approximately 2% of congenital deafness [15], while hearing loss in WS type 2 being reported by Liu *et al.* and Tagra *et al.* [12, 16] to be present in 57%, respectively 87% of cases [12, 16].

Usher syndrome is the most common cause for autosomal recessive syndromic hearing impairment [17, 18]. Our patient’s father and cousin were diagnosed with this inherited disease [19], where hearing loss is present at birth, is bilateral and profound. Its prevalence is 3.2–6.2 per 100 000 and is responsible for 3–6% of all childhood deafness [17]. It is often misdiagnosed until early signs of retinitis pigmentosa (tunnel vision/night blindness) appear.

Molecular analysis of our patient revealed the presence of the connexin 26 (W24X) gene mutation. It is reported that the connexin 26 gene is responsible for half the cases of recessive hearing loss [20].

The most obvious feature of WS of our patient was the white forelock situated on the frontal left side, which first appeared at the age of seven years. Choi *et al.* [2] reported its incidence between 17–58.4% of cases and premature graying in 7% of cases [2]. The white forelock can be present at birth or appear in early childhood, but can also disappear during adult life [17].

Skin hypopigmentation occurs in 8.3–50% of WS patients while heterochromia iridis occurs in 21–28% of cases [15]. Our case presented no hypopigmented macules on the trunk and no heterochromia. Ophthalmological examination revealed abnormal pigmentation of irides with brilliant blue irises being present bilaterally. Their coloration can be explained by the severe hypoplasia of the pigmented epithelium [6]. The patient suffers from ocular deficiency and retinal degeneration possibly inherited from his father, thus including him within the Usher syndrome limits, an autosomal recessive syndrome. Retinitis pigmentosa is a progressive, bilateral symmetric degeneration of rod and cone functions of the retina, leading to loss of night vision, constriction of visual fields, impaired visual acuity and blindness [21]. Our recommendation would be that the patient learn Braille alphabet due to progressive vision loss, which may limit communication means to only tactile signs.

Waardenburg syndrome type 2 is autosomal dominant [22]. The majority of patients diagnosed with WS have a family history [15]. In our case report, the patient also presented family history of the syndrome: mother and elder brother.

Our subjects’ eyebrows are confluent at the midline. In the study performed by Nasser *et al.* [6] it is reported that synophrys is present in 25% of WS type 2 cases [6].

In WS patients, the facial aspect is quite characteristic with hypoplastic nose, broad nasal root and hypoplastic alar cartilages, which lead to narrow nostrils [23]. Narrow nostrils could be the cause for mouth breathing in our patient. Hypoplastic alae nasi partially obstructs the naso-

respiratory system, nasal breathing becoming more difficult. Proffit *et al.* reported that a 3.5 to 4 cmH₂O/L/min. resistance to nasal airflow inclines a subject to switch to partial mouth breathing [24]. Our patient has a long face, which can be caused by mouth breathing. Proffit *et al.* also showed that in order to breath through the mouth it is necessary to lower the mandible and tip back the head, which will change the posture, increasing the facial height [24]. It is a well known fact that deleterious oral habits are one of the most frequent factors identified by orthodontists that affect the normal growth and development of muscles and jaw bones during childhood and adolescence [25]. Mouth breathing is generally associated with facial deformities such as narrow maxillary arch, high palatal vault, posterior cross bite, Class 2 dental malocclusion and upper incisor proclination [9]. Our patient presents all of the above-described features. These however are not characteristic of WS, but are consistent with it, due to mouth breathing caused by hypoplastic alae nasi. Oral manifestations of WS are not extensively described in literature. Sedani *et al.* [23] reported high arch palate, narrow maxilla and protruding lower lip in WS cases.

From a dental-orthodontic point of view, several treatments are necessary. The patient is currently undergoing dental treatment. Wearing a functional appliance was recommended for mouth breathing for one hour each day and overnight. This appliance (trainer, shown in Figure 8) may improve his dental and facial development. After all dental treatments will be performed, a fixed orthodontic appliance will be mounted. Nasal reconstruction surgery will be taken into consideration after the age of 18 years. Improving dentofacial aspects will lead to an increase of our patient's quality of life, social self-esteem and performances [26].



Figure 8 – Orthodontic functional appliance used in our case.

Congenital deafness is by far the most serious and significant clinical symptom. An early diagnosis of such a case allows for artificial cochlear implantation, a procedure that will lead to major improvements in both speech and spoken language [27].

Communication skills may be optimized if family members receive specialized training from educationers of the hearing impaired.

Orthopedic and gastroenterological examinations were mandatory for a clear diagnostic and to differentiate WS type 2 from types 3 or 4. Ophthalmological examination revealed the absence of dystopia canthorum, the main criteria to differentiate type 1 from type 2.

As shown in our study, a multidisciplinary team of medical professionals is required for diagnosis and recovery of the patient: otolaryngologist, audiologist, speech therapist, geneticist, genetic counselor, ophthalmologist, dermatologist, gastroenterologist and dentist.

Granting genetic counseling to patients' families is very important. The recurrence of WS transmission is around 50%, while in the Usher syndrome and the connexin 26 gene mutation is around 25%. Clinical features can be highly variable within families and also the degree in which a newborn will be affected by the disease.

☞ Conclusions

We reported a case of Waardenburg syndrome type 2, a very rare disease with its dental and orthodontic associated pathology caused by mouth breathing consistent with the syndrome. Our patients' congenital deafness can be explained by WS, Usher syndrome or the connexin 26 gene mutation. Our case prognosis is reserved due to the risk of deafblind and its evolution. The best recommendation would be a cochlear implant and learning of the Braille alphabet, which may bring significant benefits in the patients' quality of life.

Conflict of interests

The authors declare that they have no conflict of interests.

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