A Rare Case Report: Waardenburg Syndrome

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Abstract. Hearing loss is one of the most common congenital disorders. Hearing loss in early childhood will impair speech and language development. Waardenburg syndrome (WS) is a rare genetic disorder characterized by sensorineural deafness associated with pigmentary anomalies and various defects on neural crest derived tissues. Waardenburg syndrome is classified into four types based on their phenotypic characteristics. Clinical signs of WS include sensorineural deafness, dystopia canthorum and hypopigmentation of the iris, skin, and hair.This report presents a case of Waardenburg Syndrome at the Otorhinolaryngology Clinic, Hospital of Universitas Islam Indonesia which was found in April 2021. An 11-month-old child was referred for investigation of speech delay etiology. The mother's pregnancy history did not reveal any infection or accompanying severe disease. The patient is an only child, and no one in the family has experienced anything similar. Physical examination showed pigmentary abnormality of the iris and a flat nose bridge. An otoacoustic emission (OAE) test and Brain Evoked Response Auditory (BERA) were performed and revealed sensorineural hearing loss (SNHL).Waardenburg syndrome is a rare genetic disorder. Diagnosis can be established based on physical examination and audiology examination so that early intervention can be done to improve speech and language development.

Keywords: Waardenburg Syndrome · Sensorineural Hearing Loss · Pigmentation Defect

1 Introduction

Waardenburg syndrome is a genetic disorder that may be evident at birth (congenital). The range and severity of signs and symptoms may vary widely from case to case. However, primary features often include distinctive facial abnormalities; unusually diminished coloration (pigmentation) of the hair, the skin, and/or the iris of both eyes (irides); and/or congenital deafness. More specifically, some affected individuals may have an unusually wide nasal bridge due to sideways (lateral) displacement of the inner angles (canthi) of the eyes (dystopia canthorum) [1].

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Waardenburg syndrome affects approximately 1 in 42,000 people. It accounts for 2 to 5 percent of all cases of congenital hearing loss. Types I and II are the most common forms of Waardenburg syndrome, while types III and IV are rare. In another study, the prevalence of Waardenburg syndrome was 2,12–3,01/100.000 in 2355 children hearing loss cases; it was estimated at 1.44–2.05/100,000 population [2].

2 Case

An 11-month-old pediatric patient was brought by his parents to the ENT clinic for Brain Evoked Response Auditory (BERA) examination. The patient was referred for investigation of his speech delay etiology. At 9-month-old, the child did not react and looked at his mother's eyes when spoken to and did not try to find the sound source, even when the parents used toys that make sounds.

The mother's pregnancy history did not reveal TORCH infection or accompanying severe disease. Ototoxic drug consumption such as antibiotics was also denied. The mother only took pregnancy drugs prescribed by doctors. The child was born at 38th week, the weight was appropriate for the gestation period, the delivery was spontaneous. After birth, hearing screening was not carried out. The child received exclusive breast-feeding and started complementary food at 6-month-old. The patient is now learning to stand without a handle.

The patient is an only child, and no one in the family has experienced anything similar, but the great-grandmother has the same blue eyes as the patient. The patient is cared for directly by his mother and is often given sound stimulation such as calling directly, being invited to play, or listening to sounds.

On physical examination, the body weight was 7 kg, and the height was 75 cm. External ear examination found the right and left auricles were of normal shape and size, masses (−), skin lesions (−). Ear canal edema (−), cerumen (−), secretions (−), furuncle (−). The right and left tympanic membranes were visualized to be intact, clear color, retraction (−), perforation (−), cone of light (+) in the right ear pointed at 5 o'clock and the left pointed at 7 o'clock. On local examination, blue irises were seen in both eyes, flat nasal bridge (+), blackish hair (Fig. 1).

Audiological examination revealed that Otoacoustic Emission (OAE) examination refers on both sides of the ear, indicating bilateral outer cochlear hair cells impairment. On BERA examination, the results of the right and left ear V waves cannot be detected up to 110 dB, indicating auditory nerve dysfunction or very severe bilateral sensory neural hearing loss (SNHL) (Fig. 2).

Fig. 1. Iris heterochromia

Result: REFER Ear: Left Date: 17/04/2021								
Protocol: 2-5 kHz Screen, 3/4 for Pass Time: 16:00:29								
L1 (dB)	L2 (dB)	F1 (Hz)	F2 (Hz)	GM (Hz)	DP (dB)	NF (dB)	DP-NF (dB)	Result
64.6	55.3	3984	4875	4407	-9.9	-5.7	-4.2	Refer
73.6	61.4	3188	3891	3522	-16.4	-16.6	0.2	Refer
70.3	60.8	2438	2953	2683	2.5	-5.7	8.2	Pass
64.8	60.3	1594	1969	1771	-6.5	2.2	-8.7	Refer

Result: REFER Ear: Right Date: 17/04/2021								
Protocol: 2-5 kHz Screen, 3/4 for Pass Time: 16:02:17								
L1 (dB)	L2 (dB)	F1 (Hz)	F2 (Hz)	GM (Hz)	DP (dB)	NF (dB)	DP-NF (dB)	Result
62.5	51.4	3984	4875	4407	-17.5	-14.7	-2.8	Refer
65.6	54.9	3188	3891	3522	-14.0	-14.7	0.7	Refer
65.5	54.7	2438	2953	2683	-5.6	-14.0	8.4	Pass
66.2	55.2	1641	2016	1818	10.8	4.1	6.7	Pass

Fig. 2. OAE Examination Result

3 Result and Discussion

Waardenburg syndrome (WS) is a rare disorder that presents with four distinct subtypes. The four WS subtypes were categorized based on their phenotypic characteristics, including pigmentary defects and craniofacial dysmorphism. There are six genes involved in WS, including PAX3, MITF, EDNRB, EDN3, SNAI2, and SOX10. Phenotypic variation will be influenced by the presence or absence of one or more of these specific gene mutations, thus distinguishing the various subtypes of the disorder. This syndrome displays an autosomal dominant inheritance pattern, but WS types 2 and 4 can show an autosomal recessive inheritance pattern in which the carrier has one copy of the mutated gene without phenotypic expression. In addition, spontaneous mutations can also occur without a previous family history of mutations [3, 4]. There was no complaint of hearing loss in this patient's family, but the grandparents from the mother's side had blue eyes without hearing loss.

Type 1 Waardenburg syndrome is associated with mutations in the paired box 3 transcription factors (PAX3) gene located on chromosome 2q35. This mutation also occurs in WS 3. PAX3 binding to DNA affects regulation of gene expression and is involved in the development of the central nervous system, skeletal muscle, and neural crest-derived tissues such as cardiac tissue, melanocytes, and enteric ganglia [2]. Individuals with mild pigmentary abnormality, dystopia canthorum (broad nasal ridge) and synophrys (unibrows) were classified into WS1, whereas those with hearing loss, hand and arm defects, and pigmentary anomalies are classified into WS3. Mutations in the Microphthalmia-associated Transcription Factor (MITF) gene, located on chromosome 3p13, results in WS Type II (WS2), which is similar to WS1 but lacks dystopia canthorum. SNAIL Homolog 2 (SNAI2) mutations on chromosome 8q11 are documented to be more commonly associated with hearing loss in WS 2. Type IV is associated with mutations in the transcription factors Sry BOX10 (SOX10), Endothelin 3 (EDN3), and Endothelin Receptor Type B (EDNRB) on the chromosome. The genes involved in this subtype are all significant in the production of melanocytes and enteric ganglia, thereby patients with WS 4 are more susceptible to symptoms associated with pigmentation anomalies, hearing loss and intestinal problems coinciding with Hirschsprung's disease [4].

Some patients with WS have congenital deafness. The National Organization for Rare Disorder states that this disease accounts for 2–5% of all cases of congenital hearing loss. Hearing loss in WS is characterized by sensory neural hearing loss (SNHL), varying from mild to severe. The incidence rate of SNHL in WS also differed between

these types. About 60% of type 1 and type 3 children and about 90% of type 2 and type 4 children have SNHL. A failure of melanocyte differentiation causes this hearing loss. Melanocytes are required in the stria vascularis for normal cochlear function. Previous studies reported abnormal radiological findings in the cochlea in WS. Semicircular canal dysplasia, vestibular duct enlargement, and cochlear dysplasia have been reported. Abnormal histopathological including degeneration of the organ of Corti, stria vascularis, and saccular macula have been reported [4–7]. In this case, the patient also had SNHL as evidenced by the OAE results that refer to both sides of the ear and BERA results which revealed inability to detect V waves on both sides of the ear up to 110 dB.

Interventions for those suspected of WS subtypes I – IV should be based on thorough clinical evaluation at any point throughout the lifespan of the child. The use of screening tools and diagnostic tests will confirm the deficit. Most providers managing WS will explore the treatment of SNHL as well as issues associated with speech and language development. Early diagnosis and repair of hearing defects is very important for the psychological development of children with this disease. Interventions may include amplification devices (hearing aids), frequency-modulated systems (FM), or cochlear implant (CI) to optimize cognitive development in children with prelingual deafness, thereby improving the ability to hear language and acquire speech [1, 3].

It is recommended to perform a Cochlear Implant (CI) to catch up with speech delays in this patient. Research conducted by Polanski et al. on three children who experienced SNHL in WS who underwent CI intervention and auditory-verbal therapy. The results showed that the first and second children experienced progressive communication development, and after five years of using CI, they achieved fluent oral communication. At the same time, the third patient has not been able to do a final assessment [8].

Recent study has shown that children who experienced hearing deprivation improved three years after implantation. Age at implant was significantly correlated with receptive vocabulary at school entry, meaning that a younger age at CI was associated with higher receptive vocabulary skills when the child entered primary school. Recent recommendations suggest that implantation in the first 12 to 18-month-old improves the potential for the child to develop language at a rate similar to their normal-hearing peers. Children who received implantation after 18-month-old but less than 3-years-old also have the potential to develop language at a rate similar to their normal-hearing peers, but with a greater possibility of delay when compared with normal hearing subjects [9].

4 Conclusion

Waardenburg Syndrome is a rare genetic disorder. Waardenburg Syndrome presents with four distinct subtypes. This disease has various symptoms that depend on genotypic such as hearing loss, pigmentation disorders, dystopia canthorum, and even Hirschsprung Disease. In patients with Waardenburg syndrome, it is necessary to carry out initial screening to minimize hearing loss, which will affect the child's speech and language development.

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