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CASE REPORT

Waardenburg syndrome type I- a rare case report

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ABSTRACT

Waardenburg syndrome (WS) is an inherited autosomal dominant disorder characterized by varying degrees of hearing loss and pigmentary anomalies affecting the eye, hair, skin. It is a rare syndrome affecting about 1 in 42,000 individuals. We herein report a case of WS type I in an 8 day old neonate, which to the best knowledge of the authors is the youngest reported case in literature.

Key Words: Waardenburg syndrome, white forelock, sensorineural deafness, Piebaldism

Introduction

Waardenburg syndrome (WS), an inherited autosomal dominant disorder is characterized by varying degrees of hearing loss and pigmentary anomalies affecting the eye, hair, skin [1-6] and various defects of neural crest derived tissues [4,7,8]. WS is named after the Dutch ophthalmologist Petrus Johannes Waardenburg who described the syndrome in detail in 1951 [6]. It affects about 1 in 42,000 individuals [6]. This syndrome is both clinically and genetically heterogeneous and is classified into four variants [4]; type I, type II, type III (Klein's syndrome) and type IV (associated with Hirchsprung's disease). Of these, WS type I is one of the most common genetic causes of deafness accounting for about 2% of the congenitally deaf children [9]. Other occasional associations reported are cleft lip and palate, EEG abnormalities, epilepsy, microphthalmia, anterior lenticonus and high refractive errors [6,10]. We herein report our diagnosis of WS type I in a male neonate, who was brought to our clinic by his parents with chief complaint of white streak of hair since birth.

Case Presentation

An 8 day old, otherwise normal Indian male neonate was brought to our Out Patient Clinic by his parents with white streak of hair since birth. He was a term infant, born through vaginal delivery and first product of a non consanguineous marriage. His weight and height at birth were 3.1 kg and 51 cm respectively. His perinatal history was uneventful. There was no history of illness or drug consumption by the mother during pregnancy. Parents had no known abnormality and no positive family history of similar presentation was elicited on interview. On examination, the most striking feature was the presence of central white forelock of hair (Figure 1) as told by the parents. Careful examination of the face showed wide set eyes due to a prominent broad nasal root, also known as dystopia canthorum/telecanthus, confluence of eyebrows laterally and facial asymmetry. Mongolian spots (blue color) were seen on the lateral side of the left thigh and the lower part of the abdomen on the left side. In addition, a depigmented macule measuring approximately 1 cm in diameter on the hypothenar region with a central area of hyperpigmentation was noticed. There was no evidence of any congenital malformations. Per abdomen and cardiovascular examination were normal. With this view, a differential diagnosis of Waardenburg syndrome and Piebaldism was made on initial clinical assessment.

The neonate was then referred to Otorhinolaryngological and Ophthalmological departments for further evaluation. Brainstem Auditory Evoked Responses (BERA) showed bilateral sensory neural deafness. The inter-lateral canthus, inter-medial canthus and inter-pupillary distances were found to be 7.5 cm, 4.1 cm and 5.3 cm respectively. Fundoscopy revealed no abnormality. The corneal diameter and ocular tension were normal. Lacrimal passages were patent in both eyes with brisk pupillary reaction to light. Chest X-Ray was within normal limits. Ultrasonography of the abdomen and the pelvis showed no abnormality. Haemogram, coagulation profile, liver and renal function tests were within normal limits. No abnormality was detected on Computed Tomographic scan of head. The clinical findings were correlated with the reports of investigation, which pointed towards a definitive diagnosis of Waardenburg syndrome type I. The patient's parents were advised to get a cochlear implant for their child.

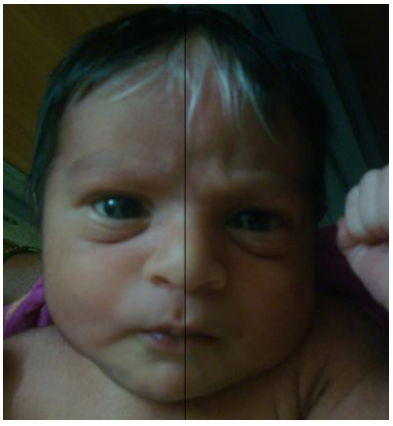

Figure 1 Showing wide set eyes due to broad nasal root (dystopia canthorum), central white forelock, confluent

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eye brows laterally and facial asymmetry on careful observation.

Discussion

WS named after Petrus Johannes Waardenburg found this syndrome in 1.4 per cent of congenitally deaf children and calculated from these data the estimated incidence to be about 1 in 42,000 in Holland [6]. Waardenburg's syndrome type I is an autosomal dominantly inherited condition, with variable penetrance and expression. Isolated cases have also been reported [11]. The exact etiology of WS has been implicated to mutations of the *PAX3* gene in WS type I and III, while *endothelin B receptor* gene or *endothelin-3* gene or the *soxio* gene have been identified in WS type IV [12-14]. In 1992, the Waardenburg Syndrome Consortium proposed a diagnostic criteria for Waardenburg syndrome type I [15] (Table 1).

Table 1 Diagnostic criteria

Major criteria	Minor criteria
Hypopigmentation of hair (White forelock)	Broad high nasal root
Pigmentary disturbances of the iris	Hypoplasia of alae nasi
Congenital sensorineural hearing loss (SNHL)	Synophrys or medial eye brow flaring
Affected first degree relative	Congenital leucoderma (several areas of hypopigmented skin)
Dystopia canthorum, with a 'W' index that exceeds 1.95	Prematurely greying hair (predominantly white by 30 years of age)

Individuals should be considered to have WS type I if they have 2 major or 1 major and 2 minor criteria from the features mentioned in table 1. In 1995, Liu et al used the same list to define WS type II [7]. Individuals with 2 major features who do not have dystopia canthorum are considered to have WS type II. In our patient, 3 major (White forelock, sensorineural hearing loss, and dystopia canthorum) and 1 minor (broad nasal root) criteria were found, thus confirming our clinical diagnosis of WS and pointing towards the variant WS type I. Neither parents nor any other member of the family had any history of pigmentary abnormalities, congenital deafness or findings suggesting WS. Thus it could be a sporadic case due to incomplete penetrance of the gene and variable expressivity [16-18]. Chang et al [19] reported Waardenburg syndrome in 2 members of a family who atypically demonstrated spontaneous pigmentation and contraction of congenital leukodermic patches. In place of a white forelock, an artificial color of red, brown, or black hair was observed, quite contrary to the diagnostic criteria. The white forelock is the most frequent cutaneous pigmentary abnormality with an incidence ranging from 17 to 58.4% [20,21]. In our patient, we noticed confluence of eyebrows laterally, which is contradictory to the diagnostic criteria and thus an unusual and atypical presentation. White macules anatomically distinct from the white forelock are also a predominant feature with an estimated prevalence of 15% [20,21]. The patches of depigmentation resemble those of Piebaldism, are present at birth, do not grow, and do not re-pigment. Hyperpigmented macules may be found within the amelanotic area. Heterochromia irides may be partial or total and is found in 20% of reported cases [20,21]. Dystopia canthorum is characterized by an increase in the distance between the inner angles of the eyelids with normal distances between the pupils and the outer canthus [22], which was consistent with our finding.

WS equally affects both sexes and all races, with no sex difference among persons with congenital deaf-mutism. Among deaf-mutes WS has been observed in 0.9-2.8 percent of cases [22]. Deafness is the most serious feature of WS. WS accounts for approximately 2-3 percent of the population with profound congenital deafness. Also, deafness is a presenting feature in approximately 25 percent of WS type I and in 50 percent of WS type II [23-25]. However, the phenotypic features of WS help to make an early diagnosis of this syndrome among deaf-mute children [5]. Earlier diagnosis means a more successful rehabilitation of hearing [22]. Histopathologic examination of the inner ears of person with Waardenburg syndrome shows absent organs of corti, atrophy of the spinal ganglion, and reduced numbers of nerve fibers [23-26]. Unlike few reports, our case did not show signs of vitiligo, craniostenosis, Hirchsprung's disease, ventriculoseptal defect, alopecia or lacrimal sac mucocoele [18,27,28]. The outward displacement of the medial canthi corresponds to the embryonic condition at the beginning of the third month of gestation [16,17]. Anomalies of pigmentation and deafness are due to developmental abnormality in the neural crest [18]. Karaman et al [29] in 2006 reported the findings of WS I in a 3 year old girl suffering from congenital deafness and mutism. Wang J et al [30] in their study on 5 unrelated Chinese patients suffering from WS found three novel and two known mutations in *PAX3*. The clinical manifestations of these 5 Chinese patients with PAX3 mutations were consistent with the phenotypes of WS1. However, pigmentary changes on skin, hair, eyebrows, and eyelashes were absent, indicating ethnic specific variations in clinical expression. Parekh et al [31] have reported a case of this syndrome in association with ventricular septal defect. Our case however has no congenital cardiac anomaly. Boporai et al described this syndrome in an 8 month old female. Our patient probably is the youngest case of WS reported so far in literature. Sujatha et al [32] reported a case wherein mucocoele, alopecia and poliosis were additional features. Porot et al [33] have suggested the addition of epilepsy to the usual symptoms of Waardenburg syndrome. However, we did not find any of the features reported by others. A screening program to detect Waardenburg syndrome throughout Columbia identified 95 affected individuals belonging to 95 families; the frequency rate of Waardenburg syndrome was 5.38% in the institutionalized deaf population [34]. All patients had sensorineural deafness, and the most common features included broad nasal root (58.9%), an affected first-degree relative (37.9%), heterochromia irides (36.8%), skin hypopigmentation (31.6%), white forelock (28.0%), intense blue iris (27.4%), synophrys (12.6%), premature graying (10.5%), ptosis of the eyelids (9.5%), and hypoplasia alae nasi (1.1%).

There is currently no treatment or cure for Waardenburg syndrome. The symptom most likely to be of practical importance is deafness, and this is treated as any other

irreversible deafness. Folic acid supplementation in pregnancy has been recommended for women at increased risk of having a child with WS type I, given the possibly increased risk of neural tube defects [35]. Cases of Piebaldism associated with heterochromia irides have been described, and may thus pose a dilemma in clinical diagnosis of WS. However the possibility of a chance association or even a distinct genetic entity cannot be ruled out. Chromosomal detection, molecular and genetic studies could not be performed due to financial constraints of the patient's family. But, considering the presence of other characteristic facial features we propose this patient to be of Waardenburg's syndrome type I [36].

Conclusion

WS being a rare syndrome needs prompt suspicion by the physician for its diagnosis. Understanding the typical and atypical phenotypes of WS is of clinical importance. Efforts for prevention and prenatal diagnosis are still in the nascent stage. Further research aimed at prenatal identification of the cause of mutations and prevention of the disease is warranted.

References

1. Hageman MJ, Delleman JW. Heterogeneity in Waardenburg syndrome. *Am J Hum Genet* 1977;29:468–85.
2. Markova TG, Megrelishvilli SM, Shevtsov SP, et al. Clinical and molecular genetic investigation of Waardenburg syndrome type I. *Vestn Otorinolaringol* 2003;1:17–9.
3. Kondoh T, Matsumoto T. Waardenburg syndrome. *Ryoikibetsu Shokogun Shirizu* 2000;30:255–7.
4. Read AP, Newton VE. Waardenburg syndrome. *J Med Genet* 1997;34:656–65.
5. Newton VE. Clinical features of the Waardenburg syndromes. *Adv Otorhinolaryngol* 2002;61:201–8.
6. Waardenburg PJ. A new syndrome combining developmental anomalies of the eyelids, eyebrows and nose root with pigmentary defects of the iris and head hair and with congenital deafness. *Am J Hum Genet* 1951;3(3):195–253.
7. Liu XZ, Newton VE, Read AP. Waardenburg syndrome type II: phenotypic findings and diagnostic criteria. *Am J Med Genet* 1995;55(1):95-100.
8. Reynolds JE, Meyer JM, Landa B, *et al.* Analysis of variability of clinical manifestations in WS. *Am J Med Genet* 1995;57:540–7.
9. Milunsky JM, Maher TA, Ito M, Milunsky A. The value of MPLA in Waardenburg Syndrome. *Genet Testing* 2007;11:179–82.
10. Pantke OA, Cohen MM Jr. The Waardenburg syndrome. *Birth Defects* 1971;7: 147.
11. Ortonne JP. Piebaldism, Waardnburg's syndrome, and related disorders: "Neural Crest Depigmentation Syndrome." *Dermatologic Clinics* 1988;6(2):205-16.
12. Tassabehji M, Newton VE, Liu XZ, *et al.* The mutational spectrum in Waardenburg syndrome. *Hum Mol Genet* 1995;4:2131–7.
13. Tachibana M. A cascade of genes related to Waardenburg syndrome. *J Invest Dermatol Symp Proc* 1999;4:126–9.
14. Lalwani A, Attaie A, Randolph F, *et al.* Mutation in the MITF gene causing WS type II in a three-generation Indian familiy. *Am JMed Genet* 1998;80:406–9.
15. Farrer LA, Grundfast KM, Amos J, et al. Waardenburg syndrome (WS) type I is caused by defects at multiple loci, one of which is near ALPP on chromosome 2: first report of the WS consortium. *Am J Hum Genet* 1992;50(5):902-13.
16. Waardenburg PJ. Intraocular-pigmentary dyspiasia. *Graefes Arch Ophthal* 1930;124:221.
17. Waardenburg PJ. Embryonic fixation syndrome. *Am J Hum Genetics* 1951;3:195.
18. Garnett AR. Waardenburg syndrome in birth defects. Encyclo-pedia. Buyse ML, Blackwell Scientific Publications, USA, 1990; 1773-74.
19. Chang T, et al. Spontaneous contraction of leukodermic patches in Waardenburg syndrome. *J Dermatol* 1993;20(11):707-11.
20. Goldberg MF. Waardenburg's syndrome with fundus and other anomalies. *Arch Ophthalmol* 1966;76:797-810.
21. Reed WB, Stone VM, Border E, et al. Pigmentary disorders in association with congenital deafness. *Arch Dermatol* 1967;95:176-86.
22. Dourmishev AL, Dourmishev LA, Schwartz RA, et al. Waardenburg syndrome. *Int J Dermatol* 1999;38:656-63.
23. Jensen J. Tomography of the inner ear in a case of Waardenburg's syndrome. *Am J Roentgenol Radium Ther Nucl Med* 1967;101:828-33.
24. Newton V. Hearing loss and Waardenburg's syndrome: implications for genetic counselling. *J Laryngol Otol* 1990;104:97-103.
25. Oysu C, Baserer N, Tinaz M. Audiometric manifestations of Waardenburg's syndrome. *Ear Nose Throat J*. 2000; 79: 704-9.
26. Merchant SN et al. Otopathology in a case of type I Waardenburg's syndrome. *Ann Otol Rhinol Laryngol* 2001;110:875-82.
27. Boparai MS, Sohi BK, Sohi AS. Waardenburg Syndrome. *Ind J Ophth* 1979;27:21-2.
28. Joseph TA, Chakravarthy KS. Waardenburg Syndrome. *Ind J Ophth* 1980; 28:37-8.
29. Karaman A, Aliagaoglu C. Waardenburg syndrome type I. *Dermatology Online J* 2006;12 (3):21.
30. Wang J, Li S, Xiao X, et al. *PAX3* mutations and clinical characteristics in Chinese patients with Waardenburg syndrome type I. *Mol Vis* 2010;16:1146–53.
31. Parekh P, Singh SD, Dulhani JD, et al. *Ind Pediat* 1976;13(6)*:*465.
32. Sujatha S, Thomas A. Waardenberg syndrome. *Ind J Ophthal* 1974;22(3);24-6.
33. Porot M, Dugas M, Duplaix A. *Rev Neuro Psychiat Infantile* 1975;23:10.
34. Tamayo ML, Gelvez N, Rodriguez M, et al. Screening program for Waardenburg syndrome in Colombia: clinical definition and phenotypic variability. *Am J Med Genet* 2008;146A(8):1026-31.
35. Fleming A, Copp AJ. Embryonic folate metabolism and mouse neural tube defects. *Science* 1998;280(5372):2107-9.
36. Comings DE, Odland GE. Partial albinism. *JAMA* 1966;195:519.

Authors' Contributions

GS, KA, DYS, SP, AD participated in the clinical diagnosis, sequence alignment, drafting the manuscript and made useful contribution in the revision of the literature. GS, DYS, NBK, SY and RG participated in writing discussion. All authors read and approved the final manuscript.

Consent

Written informed consent was obtained from the father of the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the editor-in-chief of this journal.

Competing Interests

The authors declare that they have no competing interests.

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