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Case Series

Waardenburg syndrome - Report of two cases

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ABSTRACT

Waardenburg syndrome (WS) is a group of genetically heterogeneous disorders characterised by white forelock of hair, heterochromia irides, blue eyes, and sensorineural hearing loss as main characteristics. A 3-year-old girl presented with pre-lingual deafness and mild delay in developmental milestones. Both parents were deaf since childhood. On examination, she had a white forelock, heterochromia iridium, dystopia canthorum and hypopigmented areas noted in the distal end of all four limbs. A 1-year-old girl presented with pre-lingual deafness. Other milestones are normal for age. On examination, the baby was not responding to sound, and white forelock, heterochromia iridium, dystopia canthorum and hypopigmented skin over the dorsum of hands and legs were present. Mother also has a white forelock and dystopia canthorum. Brain stem auditory-evoked potentials in both cases showed bilateral auditory pathway dysfunction. Based on the above findings, a diagnosis of WS type-1 (WS-1) was made in both and confirmed by genetic testing. Clinical features of the skin, hair changes, and hearing impairment with language delay with a family history that we should consider WS-1.

Keywords: Waardenburg syndrome type-1, Sensorineural deafness, Telecanthus, Dystopia canthorum, Irides

INTRODUCTION

Neural crest cells are multipotent cells arising near neural tubes and give rise to structures such as skin melanocytes, inner ear cells, glia, some cells of the nervous system, and craniofacial structures. Disorders of neural crest cells are termed neurocristopathies.[1,2] Waardenburg syndrome type-1 (WS-1: OMIM#193500) classified as neurocristopathies is an autosomal dominant disorder caused by mutations in the *PAX3* gene. The disorder is characterised by sensorineural hearing loss, dystopia canthorum and pigmentary abnormalities of hair, skin and eyes and is classified under auditory pigmentation disorder.[3] The disorder is clinically heterogeneous. Here, we present two cases of WS-1 from India.

CASE SERIES

Case-1

A 3-year-old girl child born to a non-consanguineously married couple at term with normal birth weight presented with unable to speak and hear. All other milestones were attained as per age. On examination, the baby was not responding to sound, white forelock, heterochromia iridium, dystopia canthorum and hypopigmented areas were noted in the distal end of all four limbs, and both the parents were deaf. Brain stem auditory-evoked potentials showed no waves suggestive of bilateral auditory pathway dysfunction. Exome sequencing revealed homozygous mutation

c.141C>G (p.Asn47Lys) in the *PAX3* gene. A diagnosis of WS-1 was made based on these findings and confirmed by genetic testing.

Case-2

One girl born to a non-consanguineously married couple with uneventful antenatal and birth history presented to us with complaints of being unable to speak or hear. Other milestones are normal for age [Figures 1a and b]. On examination, the baby was not responding to sound, and white forelock, heterochromia iridium, dystopia canthorum and hypopigmented skin over the dorsum of hands and legs were present [Figures 2a and b]. Mother also has a white forelock and dystopia canthorum. Brain stem auditory-evoked potentials showed no wave suggestive of bilateral auditory pathway dysfunction. Exome sequencing revealed homozygous mutation c.268T>C (p.Tyr90His) in the *PAX3* gene. Based on the above findings a diagnosis of WS-1 was made and confirmed by genetic testing.

In both cases, routine investigations, complete hemogram, liver function, renal function tests, magnetic resonance imaging of the brain, lactate, ammonia, arterial blood gas and Tandem mass spectrum were normal.

DISCUSSION

WS is phenotypically recognised under four types, type-1(OMIM#193500) and type-2 (OMIM#193510) have similar features except type-1 has dystopia canthorum. Type-3 (OMIM#148820) additionally has dystopia canthorum along with upper limb anomalies. Type-4 (OMIM#277580) also known as Waardenburg-Shah syndrome additionally has Hirschsprung disease (HD). Peripheral demyelinating neuropathy, central dysmyelination, WS and HD (PCWH syndrome) a subtype of type-4 have features of mental retardation, peripheral neuropathy, spasticity, and cerebellar ataxia.

Clinical features in type-1 WS include sensorineural hearing loss (47–58%), heterochromia irides (15–31%), hypoplastic blue irides (15–18%), white forelock (43–48%), early greying (23–38%), leukoderma (22–36%), high nasal root (52–100%) and medial eyebrow flare (63–73%).[4-6] The differential diagnosis considered was Piebaldism (OMIM#172800) caused due to mutations in the dominant mutations in *KIT* or *SNAI2* gene. The common features between this and WS are pigmentary changes and white forelock of hair; however, deafness and iris defects are rarely reported. The other disorder is Tietz syndrome (OMIM#103500) caused by dominant mutations in the *MITF* gene. The features common are albinism and deafness,

Farrer *et al*. suggested diagnostic criteria for WS, based on the presence of two major or one major and two minor

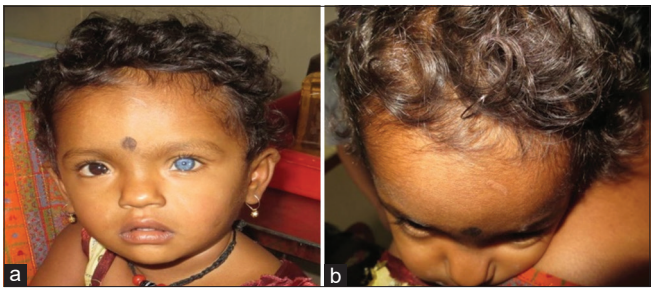

Figure 1: (a and b) Clinical photograph of case two showing white forelock, heterochromia iridium and dystopia canthorum.

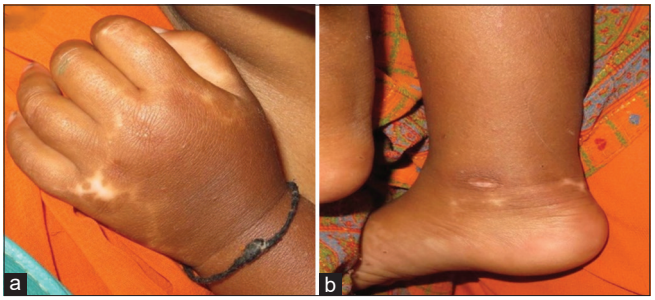

Figure 2: (a and b) Clinical photographs of case two showing hypopigmented skin over the dorsum of the hand and leg.

criteria suffices for the diagnosis of WS-1[7] and confirmed by genetic testing. In the current report, case-1 and 2 had all the five major features thus fitting the diagnosis: congenital sensorineural hearing loss, white forelock and hair hypopigmentation, heterochromia iridium and dystopia canthorum and a first-degree relative affected with the same features.

Paired box-3 (*PAX3*) gene is located on chromosome 2q35 and functions in the preservation of pluripotency of stem cells, specification of cell lineage, proliferation, and inhibition against terminal differentiation, migration and apoptosis. *PAX3* alteration is seen in many cancers like rhabdomyosarcoma. It also plays a developmental role in the nervous system, neural crest-derived cells and skeletal and cardiac tissue.[8,9] Both our cases previously reported mutation in the *PAX3* gene were noted.

CONCLUSION

A combination of sensorineural deafness, pigmentation abnormalities of skin, iris and hair with dystopia canthorum, a diagnosis of WS-1 needs to be considered.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Benish BM. Letter: "The neurocristopathies: A unifying concept of disease arising in neural crest development". Hum Pathol 1975;6:128.
2. Le Douarin NM, Kalcheim C. The Neural Crest. Cambridge: Cambridge University Press; 1999.
3. Pingault V, Ente D, Dastot-Le Moal F, Goossens M, Marlin S, Bondurant N. Review and update of mutations causing Waardenburg syndrome. Hum Mutat 2010;31:391-406.
4. Liu XZ, Newton VE, Read AP. Waardenburg syndrome Type II: Phenotypic findings and diagnostic criteria. Am J Med Genet 1995;55:95-100.
5. Pardono E, van Bever Y, van den Ende J, Havrenne PC, Iughetti P, Maestrelli SR, *et al*. Waardenburg syndrome: Clinical differentiation between Types I and II. Am J Med Genet A 2003;117A:223-35.
6. Tamayo ML, Gelvez N, Rodriguez M, Florez S, Varon C, Medina D, *et al*. Screening program for Waardenburg syndrome in Colombia: Clinical definition and phenotypic variability. Am J Med Genet A 2008;146A:1026-31.
7. Farrer LA, Grundfast KM, Amos J, Arnos KS, Asher JH, Beighton P, *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;50:902-13.
8. Kubic JD, Young KP, Plummer RS, Ludvik AE, Lang D. Pigmentation PAX-ways: The role of Pax3 in melanogenesis, melanocyte stem cell maintenance, and disease. Pigment Cell Melanoma Res 2008;21:627-45.
9. Wang Q, Fang WH, Krupinski J, Kumar S, Slevin M, Kumar P. Pax genes in embryogenesis and oncogenesis. J Cell Mol Med 2008;12:2281-94.

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