

Waardenburg's Syndrome

Case Report and Review of the Literature

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SUMMARY

A case of Waardenburg syndrome (WS) is described in a 16 year old boy who presented with hetero-chromic irides, congenital deafness, white forelock and piebaldism like hypopigmented macules on dorsum of his hands, forearms and upper right chest since birth.

CASE REPORT

A 16 years old male student, presented to skin out patient department, Shaikh Zayed Hospital in January 1999 with complaints of white and dark patches on his hands and forearms since birth. He was unable to hear with his right ear since childhood. His general and systemic examinations were normal. There were similar patches on his sister's legs since birth.

Examination of his skin (Fig. 1) revealed white forelock with underlying white scalp skin. The nasal root was prominent. There was hyperplasia of medial eyebrows. Both irides were heterochromic. There were freckles on the malar area of the cheeks and nasal bridge. Hypo and hyperpigmented macules of "dappled appearance" resembling those of piebaldism were present on dorsum of both hands (Fig. 2), forearms and right side of chest. The hair within these macules were also white.

Ophthalmological examination revealed that visual acuity was markedly reduced in the right eye than the left which improved slightly with glasses. Pressure in both eyes was normal. Right iris was brown in colour with hypopigmented patches, whereas left iris had hypopigmented patches all over. On fundoscopic examination right disc margins were clear whereas left disc margins were blue with generalized hyperaemia of retina.

Puretone audiometry showed profound sensorineural hearing loss in the right ear and mild mixed type of hearing loss in the left. Routine laboratory investigations including

haemoglobin, TLC, DLC and ESR were normal. Other tests including blood urea and creatinine, LFTs and urine were normal.

DISCUSSION

Auditory pigmentary syndromes are caused by the physical absence of melanocytes from the skin, hair, eyes, or the stria vascularis of the cochlea. The inheritance of such disorders is autosomal dominant and they are labeled as Waardenburg's syndromes.

In 1951 Pal Waardenburg, a Dutch ophthalmologist described a genetically determined syndrome, of which unilateral deafness was a marked feature.

WS is characterized by lateral displacement of the inner canthi and lateral puncti, prominence of the nasal root and of the medial eye brows, congenital deafness, heterochromic irides, white forelock and hypomelanotic macules. WS shows high variability in expressivity within families and there is a difference in penetrance of clinical traits between families. WS accounts for over 2 percent of causes of all congenital hearing losses¹.

The incidence of signs of these syndromes is shown below:-

1. Wide nasal root (65%),
2. Confluent eye brows (50%).
3. Partial or complete heterochromia of iris (25%).



Fig. 1: WS; White forelock, prominent nasal root, hyperplasia of medial eyebrows, heterochromic irides, freckles on the malar area.



Fig. 2: WS; Hypo & hyperpigmented macules of "dappled appearance" on dorsum of both hands & forearms.

4. Partial albinism as white forelock (20%)
5. Congenital hearing loss (25%).
6. Depigmentation of skin (10%)
7. Hypofunction of vestibular system (75%)
8. Lateral displacement of inner canthus exists in all types of cases, but lack of lateral displacement of inner canthus is characteristic in type-II WS.

Abnormal patterns of hair growth have been noted in several cases. Some men had developed a conspicuous growth of terminal hair on the tip of the nose and in some the beard had covered the entire cheeks.

The observation of heterogeneity has given rise to segregation of WS into several types.

- **Type-I WS** is associated with dystopia canthum which is caused by loss of function and mutation in PAX3 gene².
- **Type-II WS** is a heterogeneous group. About 15% of whom are heterozygous for mutations in MITF (microphthalmia associated transcription factor) gene³⁻⁴.
- **Type-III WS** is the one originally described by Klein with blue irides, dystopia canthorum, medial eye-brow hyperplasia, bilateral labyrinthine deafness, musculoskeletal abnormalities of the upper extremities and in most, macular pigmentary dilution of the skin and hair. Some but not all patients are homozygotes².
- **Type-IV WS** (Sahah-WS with Hirschsprung disease) can be caused by mutations in the genes for endothelin-3 or one of its receptors, FDNRR4

Ultra-structure studies on the amelanotic skin show absence of melanocytes. In the pigmented areas, there are abnormalities of the melanocytes and melanosomes.

WS is associated with abnormal deposition of tyrosin causing hearing loss⁵.

Melanocytes initially appear usually by the 18th gestational week. Many specific gene products are sequentially made and utilized by the melanocytes as it emigrates from its embryonic origin to the specific target sites, synthesizes melanin within a specialized organelle, transfers pigment granules to neighboring cells and responds to various exogenous causes. A mutation in many of the respective encoding genes can result in hypopigmentary disorders. A subset of neural crest derived cells emigrate from the dorsal surface of the neural tube, become committed to the melanoblast lineage and are targeted along the dorsal lateral pathways. The specific transcription factors PAX3

and MITF appear to play a regulatory role in early embryonic development of the pigment system and in associated diseases e.g. WS3.

Pathology of inner ear reveals total absence of Organ of Corti, atrophy of the stria vascularis and absence of neurons of spiral ganglion.

Since original description over 1200 cases of syndrome have been reported not only in patients of Dutch origin, but English, American, Africans, Indians, Oriental and Negroid population is also at risk. Three cases of WS were reported from Iran⁶ in 1997. Two studies from Karachi, Pakistan^{7,8} also document this rare syndrome.

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