



WAARDENBURG SYNDROME TYPE I – A CASE SERIES FROM A SINGLE FAMILY

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ABSTRACT

Waardenburg syndrome is a rare autosomal dominantly inherited genetic disorder with non progressive audio pigmentary defect along with dystopia canthorum. The diagnosis is clinical and should be considered if an individual has 2 major or 1 major plus 2 minor criteria. In this article we report 9 cases of Waardenburg syndrome in a single family spread over 4 generations which include a pair of monozygotic twins.

KEYWORDS: Waardenburg syndrome, heterochromia iridis, hypopigmented skin patches, white forelock, sensorineural hearing loss.

INTRODUCTION

Waardenburg syndrome is a rare genetic disorder with an incidence of 1 in 42000 to 50000 population accounting for 2 – 5 % of all cases of congenital hearing loss. In 1951, Waardenburg, a Dutch ophthalmologist and geneticist, described a rare non progressive audio pigmentary disorder along with dystopia canthorum which is an autosomal dominantly inherited disorder with variable penetrance.^[1] We report 9 cases of Waardenburg syndrome type 1 in a single family which include a pair of monozygotic twins.

CASE REPORT

Index case

A just born female monozygotic twins born at 36 weeks gestation to a second gravida mother with preeclamptic toxemia and prolonged rupture of membranes were admitted in NICU with respiratory distress. They were managed with bubble CPAP and supportive care and recovered within 72 hours. Twins are second in birth order and born to a second degree consanguineous couple with positive family history of white forelock and sensorineural hearing loss running for 4 generations (illustrated in pedigree chart Figure I). Both babies had white depigmented hair over mid frontal scalp and few hypo pigmented patches of varying sizes with sharp and irregular border over abdomen and extremities (Figure II & III). Neurological examination was normal and age appropriate. Ophthalmological examination showed normal iris, fundus, canthi and intercanthal distance. Hearing screening with OAE and BERA was normal for both babies. Lab investigations were within normal limits. MRI brain revealed normal study. Based on these clinical features and family history babies were diagnosed as Waardenburg syndrome type I.

Clinical features in other family members are described below; Elder sibling, father, paternal aunt and paternal grandfather have sensorineural hearing loss, while white forelock is seen in father, paternal grandfather and great grandfather. Two of the cousins have heterochromia iridis. Genetic testing could't be done due to financial constraints.

PEDIGREE CHART

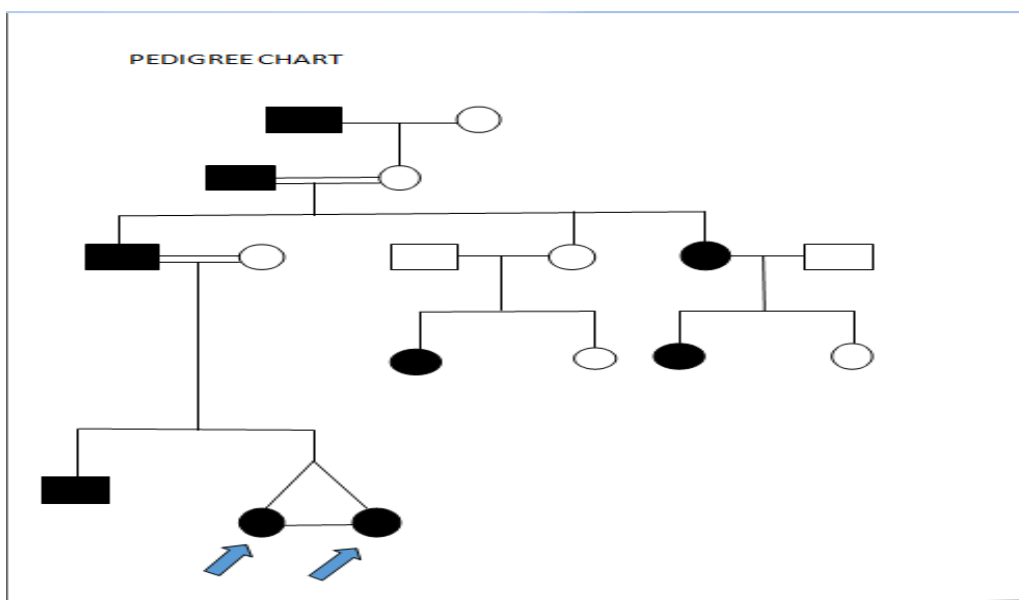


Figure I: Family pedigree chart of four generations.



Figure II: Monozygotic twins with white forelock



Figure III: Hypopigmented patch over abdomen.

DISCUSSION

Waardenburg syndrome I is an autosomal dominantly inherited disorder with variable penetrance and expression. The diagnosis is established by clinical criteria proposed by Waardenburg Consortium [Farrer et al 1992].

DIAGNOSTIC CRITERIA

Diagnosis of Waardenburg syndrome type I is considered if patient has 2 major or 1 major plus 2 minor criteria.

Major criteria

- Congenital sensorineural hearing loss
- White forelock, hair hypopigmentation
- Pigmentation abnormality of the iris:
- Complete heterochromia iridum (irides of different color)
- Partial/segmental heterochromia (two different colors in same iris, typically brown and blue)
- Hypoplastic blue irides or brilliant blue irides
- Dystopia canthorum, W index >1.95
- Affected first-degree relative

Minor criteria

- Skin hypopigmentation (congenital leukoderma)
- Synophrys/medial eyebrow flare
- Broad/high nasal root, prominent columella
- Hypoplastic alae nasi
- Premature gray hair (age <30 years)

Hearing loss: Hearing loss in Waardenburg syndrome I is of congenital sensorineural type, nonprogressive and may be unilateral or bilateral. Penetrance of mutant gene causing deafness in Waardenburg syndrome is only 20%. This explains why most of the people with this syndrome have normal hearing as in our proband.

Pigmentary abnormalities: White forelock is the commonest hair pigmentation anomaly seen in WS. It may be present at birth or appear later and may become normally pigmented over time. Red and black forelocks have also been described.^[2] The hypopigmentation can also involve the eyebrows and eyelashes.

Complete or segmental heterochromia or hypoplastic or brilliant blue irides are common ocular findings. Iris and choroidal hypopigmentation has been described.^[3]

Congenital leukoderma (white skin patches) with hyperpigmented borders are frequently found on face, trunk or limbs.

Cleft lip and cleft palate, spina bifida^[4] and vestibular symptoms are identified in some families.

There is variation in the phenotypic features in the present family members with WS 1. Even within a family, variation in clinical features may be genetic in origin or there is no phenotype genotype correlation.

GENETICS

Mutations in melanocyte cluster genes can produce effects which are quite variable and exhibit considerable phenotypic overlap. Melanocyte cluster genes include *PAX3*, *KTI*, *MITF*, *SOX10*, *endothelin 3 gene* and *endothelin 3 receptor gene e.t.c.*,^[5]

More than 90 % of patients with WS I have mutations at the *PAX 3* gene locus at 2q35. Majority are autosomal dominantly inherited and minority are due to denovo mutations which are estimated to be at the rate of 4 / 1, 00,000 and advanced paternal age can effect in new mutations.

WS I is a neurocristopathy with *PAX3* gene being expressed in neural crest, which explains the occurrence of spina bifida in several families with WS I.

WS2–*MITF* gene mutations have been described in 10–20 % of WS2. SNHL and heterochromia iridis are the two most characteristic features of WS2. Both are more common in WS2 than in WS1. White forelock and leukoderma are more common in WS1 than in WS2. W index > 1.95 is characteristic of WS1 and if average W index in a family is < 1.95 the diagnosis of WS2 is more likely.^[6]

In present case scenario proband cases showed W index < 1.95 but the average W index in the family couldn't be calculated as the older generations couldn't be examined.

WS 3 (Klien– Waardenburg syndrome) can result from homozygosity for *PAX 3* gene mutation. Individuals with WS3 have features of WS1 and hypoplasia / contractures of limb muscles or joints, carpal bone fusion, syndactyly. Craniofacial- deafness- hand syndrome due to missense mutation in *PAX 3* gene is apparently different from WS1 & WS3 with flat facial profile, hypoplastic nose and SNHL.

WS4 is due to mutations in *ED3*, *EDNRB* and *SOX10* genes. They have Hirschsprungs disease in addition to WS1 features.^[5]

MANAGEMENT

Whereas pigmentation abnormalities do not herald any survival problem, hearing loss seems to be the most important prognostic factor because of impairment of quality of life and poor cognitive abilities. Early screening for hearing problem and cochlear implant can help in normal language development.

Peri-conceptual folic acid supplementation is recommended for women with family history of Waardenburg syndrome because of increased risk of neural tube defects in association with WS.

CONCLUSION

As Waardenburg syndrome is autosomal dominantly inherited disorder, counselling of parents in affected families about 50% risk of having affected child can help them in decision making.

Although prenatal testing can identify *PAX3* gene mutation in fetus in high risk cases, it cannot determine the clinical features and their severity. Prenatal testing for conditions which do not affect the intellect or life span is not common.

Early screening of newborns for SNHL and referral for cochlear implantation or hearing aids and speech therapy can help them in language development and to lead a normal life.

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