Waardenburg Syndrome

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Abstract

Waardenburg syndrome is a rare genetic disorder characterized by varying degree of deafness associated with pigmentary anomaly and defects of neural crest cell derived structures. Four distinct subtypes showing marked interfamilial and intrafamilial variability have been described. We report a girl showing constellation of complete heterochromia, dystopia canthorum, white forelock, and synorphys. Other affected family relatives with heterochromia have been depicted in pedigree.

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Waardenburg syndrome (WS), was originally described as a syndrome with six characteristic features; lateral displacement of the medial canthi, broad and high nasal root, hypertrichosis of medial part of eyebrows, partial or total heterochromia iridis, white forelock and congenital deaf-mutism. The condition described originally is now categorized as WS type 1. Since then, four subtypes (I to IV) with variable penetrance of different clinical features have been described.1 Out of five major and five minor criteria of waardenberg syndrome either two major or one major plus two minor criteria must be present for diagnosing WS 1,2 WS III is similar to type I with additional musculoskeletal abnormalities. WS IV is associated with Hirschsprung disease.1,3 We report a young girl showing features of WS with her pedigree chart showing variable penetrance of features and hence marked intrafamilial variation of expression of WS.

Case Report

A 12 year old girl presented to out patient department with chief complaints of difference in colour of her eyes with decreased vision in left eye (Figure 1). Her unaided visual acuity at presentation was 20/20 Right eye (OD) and 20/60 left eye (OS) improving to 20/20 OS with -1.25 DSph. She was the second child of nonconsanguineous marriage with healthy siblings (2 brothers and one sister). Her birth history and development history was not remarkable. On Systemic examination, she was moderately built with average height, weight and normal intelligence quotient (IQ). She had centrally placed white forelock in frontal area (artificially dyed for cosmetic reasons) without any associated depigmentation of scalp or elsewhere on body. Her ENT and abdominal examination was within normal limits. On ocular examination, horizontal palpebral fissure was smaller in both the eyes (25 mm) along with lateral displacement of canthi. She also had broad nasal root, dystopia canthorum with interpupillary distance of 50mm and innercanthal distance of 35 mm. Medially sclera was visible to lesser extent however hirschberg corneal reflex was central. Lacrimal system was patent on syringing. Complete heterochromia with blue hypoplastic iris was noted in left eye (Figure 2). Rest of the anterior segment examination was normal in both the eyes. Pupillary reactions were normal. Right fundus was normal whereas Left fundus was albinoic showing hypopigmentation (Figure 3). Pedigree of index case was traced by interviewing her grandmother as depicted by symbols. It appeared to be an autosomal recessive inheritance with variable expressivity for heterochromia.(Figure 4)

Discussion

Waardenburg syndrome is a rare disease characterized by deafness in association with pigmentary anomalies and defects of neural crest-derived tissues. It is characterized...
by clinical manifestations of oculocutaneous anomalous pigmentation, deafness of varying degree, dystopia canthorum and broad nasal root. There are four clinical subtypes of Waardenburg depending on the presence of various clinical features. There are five major and five minor criteria for waardenburg syndrome. Major criteria include sensorineural hearing loss, iris pigmentary abnormality, hair hypopigmentation, dystopia canthorum and first-degree relative previously diagnosed with Waardenburg syndrome. Minor criteria include skin hypopigmentation, medial eyebrow flare (synophrys), broad nasal root, hypoplasia alae nasi, and premature graying of the hair. According to the diagnostic criteria proposed by the Waardenburg consortium, a person must have two major or one major plus two minor criteria to be diagnosed as WS type 1. WS2 lacks dystopia canthorum. WS3 is similar to WS1 but it is associated with upper limb defects. WS3 is the rarest form of WS. WS4 is associated with Hirschprung disease. Present case had 4 major criteria and 2 minor criteria of waardenburg type 1. Dystopia canthorum is a crucial feature for diagnosing WS type 1 which differentiates it from WS2. Dystopia canthorum is confirmed by calculating W index (in mm). W index is calculated as follows:

\[ W = \frac{X + Y + a/b}{c} \]

\[ X = \frac{2a - (0.2119c + 3.909)}{c} \]
\[ Y = \frac{2a - (0.2479b + 3.909)}{b} \]

Inner canthal distance (a), interpupillary distance (b) and outer canthal distance (c)

W index greater than 1.95 is considered abnormal. W index was 2.16 in this case. Hearing loss which is a major criteria was not present in this case. This is not a universal feature of WS but penetration study of sensorineural deafness showed 69% penetrance in WS1 and 87% in WS2. WS I and II are autosomal dominant in most of cases. WS III is usually sporadic but when it occurs in families, inheritance is autosomal dominant. Type IV is probably autosomal recessive and associated with Hirschsprung’s disease. Multiple genes have been implicated in the syndrome. Abnormalities in the PAX3 gene accounts for most of WS1 and WS3 patients. MITF (microphthalmia associated transcription factor) gene abnormality is responsible for WS2. WS4 is heterogeneous, with reported mutations in EDN3 (endothelin 3), in its receptor EDNRB (endothelin receptor type B), or in SOX10 (SRY-sex determining region Y). We could not perform PAX3 sequence but it appeared to be autosomal recessive with variable penetrance, because of healthy parents but involved family members.

References

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