Waardenburg-Shah Syndrome; A Case Report and Review of the Literature

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Abstract

Objective: Waardenburg syndrome is a rare disease characterized by sensorineural deafness in association with pigmentary anomalies and defects of neural-crest-derived tissues. Depending on additional symptoms, WS is classified into four types, WS1, WS2, WS3 and WS4. Waardenburg syndrome type 4, also called Waardenburg-Shah syndrome, is a very rare congenital disorder with variable clinical expression, characterized by Hirschsprung disease, and abnormal melanocyte migration, resulting in pigmentary abnormalities and sensorineural deafness.

Case Presentation: This report describes a five-day-old female newborn with Waardenburg's syndrome associated with aganglionosis of the colon and terminal ileum, and review the relevant literature for draws attention to the causal relationship between these two entities.

Conclusion: Different symptoms of Waardenburg syndrome appear in different people. Some individuals will require no treatment, while other may need treatment or surgery for other abnormalities. Our case had other unusual feature (bilateral external ear agenesis) we did not find any similar finding in review the relevant literature.

Key Words: Waardenburg-Shah syndrome; Hirschsprung disease

Introduction

Waardenburg syndrome (WS) is a rare (1/50,000) disease characterized sensorineural deafness in association with pigmentary anomalies and defects of neural-crest-derived tissues[1]. Depending on additional symptoms and on the basis of presence or absence of dystopia canthorum, WS is classified into four types, WS1, WS2, WS3 and WS4[2]. WS equally affects both sexes and all races[1,2]. There are five major and five minor diagnostic criteria for Waardenburg syndrome. Major criteria include sensorineural hearing loss, iris pigmentary abnormality (two eyes different color or iris...
bicolor or characteristic brilliant blue iris), hair hypopigmentation (white forelock or white hairs at other sites on the body), dystopia canthorum (lateral displacement of inner canthi) and first-degree relative previously diagnosed with Waardenburg syndrome. Minor criteria include skin hypopigmentation (congenital leukoderma/white skin patches), medial eyebrow flare (synophrys), broad nasal root, hypoplasia alae nasi, and premature graying of the hair (before age 30). An individual must have two major or one major plus two minor criteria to be considered\[^3\]. Waardenburg syndrome type 4 or Waardenburg-Shah syndrome (association of Waardenburg syndrome with Hirschsprung disease) is a very rare congenital disorder that occurs in all races, only 48 cases are reported in English literature till 2002\[^4,5\]. Several hypotheses have been advanced to explain all the clinical features of the syndrome\[^6-10\]. The deficient neural crest theory, suggesting a developmental abnormality of the neural crest as a cause of the disease, the association of Waardenburg syndrome and congenital aganglionic megacolon supports this hypothesis\[^10\]. This association can be explained by the occurrence of migration of cells from the embryonic neural crest to produce melanocytes, the adrenal ganglia, sympathetic ganglia, and sensory components of the spinal and cranial nerves\[^11\]. Since neural crest cells also migrate to the visceral ganglia of the gastrointestinal tract, it is possible that pigmentary anomalies could be associated with anomalies of the ganglion cells in the viscera\[^11,12\].

**Case Presentation**

A 5-day-old full term female neonate was admitted in neonatal ward with constipation, bilious vomiting and abnormal facieses. Her prenatal, natal and postnatal histories were within normal limits. She was the second child of consanguineous parents. She has one healthy brother. Her height, weight and head circumference were normal. On Physical examination, she had abdominal distension, central white forelock of hair with poliosis of both the upper and lower eyelashes of both eyes and medial eyebrow, bilateral external ear agenesis, road nasal root, synophrys, low anterior hairline, blue irises with left heterochromia (Fig 1). Profound bilateral sensory neural hearing loss was noted on auditory brainstem response. A clinical diagnosis of Shah-Waardenburg syndrome or Waardenburg syndrome type 4

![Fig 1](image1.png)
was made. The abdominal roentgenogram revealed dilated bowel loops but no air-fluid levels. Barium enema showed a featureless normal caliber colon with no obvious transitional zone; the small bowel loops were distended. Exploratory laparotomy was undertaken on tenth day of life that revealed distended proximal jejunal and ileal loops, the 15 cm of terminal ileum and the colon were contracted. Multiple sero-muscular biopsies were taken from colon and terminal ileum. A ileostomy was performed at the transition zone. The histopathology of gut biopsies confirmed aganglionosis in colon and terminal ileum.

Discussion

Waardenburg syndrome (WS) was first described in 1951.[13] There are 4 types of this syndrome[14]. Type 4 is Waardenburg-Shah syndrome[4,11,12,15]. The multiple types of this syndrome result from mutations occurring in different genes[6,8,10,15-17]. All types share 2 dominant features: hearing loss and partial albinism[1-18].

Our case had bilateral sensory neural hearing loss, partial albinism, abdominal distension, poliosis of both the upper and lower eyelashes of both eyes and medial eyebrow, bilateral external ear agenesis, road nasal root, synophrys, low anterior hairline and blue irises with left heterochromia. WS4 is the association of Waardenburg syndrome with Hirschsprung disease[6,8,10,15-17]. Only 48 cases are reported in English literature till 2002[4]. We had not find any type of Waardenburg-Shah syndrome in Iranian literature. The clinical and histopathologic finding in Our case confirmed Waardenburg syndrome with Hirschsprung (WS4). Waardenburg syndrome is autosomal dominant for most persons with types I, II, or III. Waardenburg syndrome type IV is autosomal recessive with variable penetrance and is due to SOX10 or endothelin-B receptor (EDNRB) genes mutations, which appear to correlate with the intestinal and/or neurological symptoms manifested in patients[8,10,15-17].

Our patient has one healthy brother and normal parents with consanguineous marriage. She had no positive family history hence it could have been a sporadic case due to incomplete penetrance of the gene and variable expressivity. Babies born with Waardenburg syndrome may have the characteristic hair and skin changes and hearing loss. However, if the symptoms are mild, Waardenburg syndrome may go undiagnosed until a family member is diagnosed and all family members are examined. Formal hearing tests can be used to detect hearing loss[19].

Our patient had profound bilateral sensory neural hearing loss on auditory brainstem response. Different symptoms of Waardenburg syndrome appear in different people, even within the same family. Some individuals will require no treatment, while other may need treatment or surgery for other abnormalities. No special diet or activity restrictions are needed[1,18]. Waardenburg syndrome does not usually affect the mind. Folic acid supplementation in pregnancy has been recommended for women at increased risk of having a child with WS[20]. Inheritance of types 3 and 4 is more complex, but genetic counseling can help assess the risk of passing Waardenburg syndrome on to a child[15,17,18,20]. This case belonged to Waardenburg Type 4 since there was evidence of Hirschsprung disease association with Waardenburg syndrome.

Our case did not show signs of limb abnormalities and dystopia canthorum. Our case had other unusual feature such as bilateral external ear agenesis; we did not find any similar finding in review the relevant literature.

Conclusion

Different symptoms of Waardenburg syndrome appear in different people. Some individuals will require no treatment, while
other may need treatment or surgery for other abnormalities. Folic acid supplementation in pregnancy has been recommended for women at increased risk of having a child with WS. Our case had other unusual feature (bilateral external ear agenesis) we did not find any similar finding in review the relevant literature.

References