

Association of Hirschsprung disease with Waardenburg syndrome and role of gene studies: A review of 2 cases

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ABSTRACT

Background: Waardenburg-Shah syndrome type 4 is an association of Waardenburg syndrome with Hirschsprung disease. Three disease-causing genes have been identified so far: Endothelin receptor type B encoding the endothelin-B receptor, EDN3 encoding an endothelin receptor ligand and Sry-like HMG box10 (SOX10) encoding the SOX10 transcription factor. **Case Report:** This is a review of 2 cases with variable onset of presentation and extent of aganglionic segment. **Intervention/Outcome:** In case 1, primary pull-through, as definitive surgical correction was done as a single procedure, whereas in case 2, required ileostomy with a plan of definitive surgery later on. **Message:** Mutation studies are helpful in characterization of the syndrome and counseling to the family. Furthermore, prognosis depends on the length of the ganglionic segment.

Key words: Autosomal recessive disorder, Endothelin receptor type B, Sensorineural deafness, Short-segment Hirschsprung disease, Sry-like HMG box10, Waardenburg syndrome

Waardenburg-Shah syndrome type 4 (WS4) is a neurocristopathy characterized by the association of Waardenburg syndrome (sensorineural hearing loss and pigmentary abnormalities) and Hirschsprung disease [1]. Patients present in the neonatal period with pigmentary anomalies (white forelock, white eyebrows and eyelashes, white skin patches, and pigmentary anomalies of the irides) and intestinal obstruction [1,2]. Sensorineural deafness is common and early and may be unilateral. Several gene alterations have been described such as EDN, EDNB, and Sry-like HMG box 10 (SOX10) genes [3]. Clinical profile of the patients varies according to the genetic alteration they are carrying. Manifestation of the intestinal obstruction depends on the length of the involved segment in Hirschsprung disease. Long segment involvement presents with intestinal obstruction from the first few days of life, whereas those with short-segment involvement manifest later [4]. We report a series of 2 cases of WS4, who had the variable onset of presentation.

CASE REPORTS

Case 1

A 12 day old, full-term male baby with birth weight of 3.1 kg, born to a primigravida with history of the 2nd degree consanguineous marriage presented with a history of the delayed passage of

meconium beyond 48 h, progressive abdominal distension since the 4th day of life, and repeated vomiting episodes which were gradually turning to bilious. On examination, he had white forelocks, white eyebrows and eyelashes, heterochromia irides, and distended abdomen (Fig. 1). Plain abdominal radiographs showed dilated loops of bowel with an absent rectal gas shadow (Fig. 2). Initially, he was managed by decompressing the dilated bowel with rectal washout using small volume of warm saline. Definitive surgical correction was performed as a single procedure of primary pull-through (Table 1). Multiple seromuscular biopsies taken intraoperatively revealed aganglionosis in the rectum and sigmoid colon compatible with a diagnosis of short-segment Hirschsprung disease. BERA detected sensorineural hearing loss in right ear. Gene studies identified homozygous mutation of endothelin receptor type B (EDNRB) (13q22.3) gene while parents were carrier of this gene with next-generation sequencing (NGS) method.

Case 2

A 3-day-old female, full-term neonate, was admitted with progressive abdominal distension and inability to pass meconium since birth. She was a 2nd child born to a 30-year-old mother with a history of the 3rd degree consanguineous marriage. Her weight, head circumference, and length were between 25th and 50th percentile for the age. She had a 6-year-old elder sibling.

Her father, uncle, and elder sibling had heterochromia irides. On examination, white forelock, white eyebrows, heterochromia irides, and distended abdomen were found (Fig. 3). Abdominal X-ray revealed few dilated bowel loops with air-fluid level and relatively gasless lower abdomen (Fig. 4). Barium enema showed a featureless small caliber colon with no obvious transitional zone; the small bowel loops were distended (Fig. 5). Exploratory laparotomy, done after a period of fluid management and decompression of the bowel, revealed distended jejunum and ileal loops, transition zone at mid-ileum level, and collapse of terminal ileum and colon. Multiple seromuscular biopsies showed muscle coat with the absence of ganglion cells and hypertrophied nerve bundles in ascending, transverse, and sigmoid colon. Ileostomy was made at the transition zone with the plan of definitive surgery and subsequent stoma closure later on (Table 1). Hearing impairment was detected in both ears by BERA and gene studies revealed Sry-like HMG bOX (SOX) 10 mutations in father and the baby by NGS method.

DISCUSSION

WS4 is caused by abnormal migration or differentiation of neural crest cells during embryonic development. It affects an estimated 1 in 40,000 people and accounts for 2–5% of all cases of congenital hearing loss [1,3]. Types I and II are the most common forms of Waardenburg syndrome, while Types III and IV are rare [3]. Waardenburg syndrome is named after the investigator (P J Waardenburg) who first precisely described the disorder in 1951 [4]. Diagnosis of Waardenburg syndrome

requires two major or one major plus two minor criteria. The major criteria include sensorineural hearing loss, iris pigmentary abnormalities (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 1st-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) [3,4].

Diagnosis is based on the recognition of the clinical picture and can be confirmed by identification of a mutation in one of the disease-causing genes. Three disease-causing genes have been identified so far: EDNRB (13q22.3) encoding the endothelin-B receptor, EDN3 (20q13.32) encoding an endothelin receptor ligand, and SOX10 (22q13.1) encoding the SOX10 transcription factor [5]. Mutations in the EDNRB and EDN3 genes are inherited in an autosomal recessive manner, in which individuals carrying homozygous mutations manifest WS4 and those with heterozygous mutations in either gene present with isolated Hirschsprung disease or often being asymptomatic [6]. Most often, the parents of an individual with an autosomal recessive condition, each carry one copy of the mutated gene, do not show signs and symptoms of the condition. This explains our first case which had EDNRB homozygous mutation and both parents were carrier and lacked any features of WS4 syndrome.

SOX10 mutations are inherited in autosomal dominant (AD) manner and specific mutations (particularly those involving the 2 terminal coding exons) appear to result in a more severe WDS



Figure 1: White forelocks, white eyebrows and eyelashes, and distended abdomen



Figure 2: X-ray abdomen showing dilated loops of bowel with an absent rectal gas shadow

Table 1: Clinical profile of two cases

Cases	Sex	Family member with Waardenburg's syndrome	Gene mutation studies	Extent of involvement	Surgery
Case 1	Male	None	EDNRB (13q22.3)	Short-segment (rectum and sigmoid colon)	Primary pull-through
Case 2	Female	Father, uncle, and elder sibling (heterochromia irides)	SOX10 (22q13.1)	Total colonic aganglionosis	Ileostomy with definitive surgery and stoma closure later on

EDNRB: Endothelin receptor type B, SOX10: Sry-like HMG bOX10



Figure 3: White forelock, white eyebrows, and ileostomy wound



Figure 4: Abdominal X-ray showing few dilated bowel loops with air-fluid level and relatively gasless lower abdomen



Figure 5: Barium enema revealing a featureless small caliber colon with no obvious transitional zone and distended small bowel loops

variant with neurologic findings characterized by peripheral demyelinating neuropathy, central dysmyelinating leukodystrophy, Waardenburg syndrome, and Hirschsprung disease. Some patients with type 2 Waardenburg syndrome (Waardenburg syndrome without Hirschsprung disease) are carriers of heterozygous SOX10 mutations [7,8]. The 2nd infant in this series and her father

had SOX10 mutation. Family history of heterochromia irides and the absence of Hirschsprung disease can be explained by variable expression characteristic of AD disorders.

A number of disorders may be considered in the differentials such as partial albinism and deafness; familial cases of vitiligo and congenital sensorineural deafness and Vogt-Koyanagi-Harada syndrome which is characterized by inflammatory conditions of the eyes, vitiligo; whitening of the eyebrows, eyelashes, and scalp hair (poliosis), alopecia, and dysacusis [9].

WS4 may be diagnosed at birth or early childhood based on the identification of characteristic physical findings, a complete patient and family history. Diagnostic evaluation may include calculation of W-index (for presence or absence of dystopia canthorum) in which the distances between the inner canthi, the outer canthi, and the pupils (interpupillary distances) are analyzed [9]. Additional diagnostic studies that may be considered include a slit-lamp examination of eyes, and CT to evaluate the inner ear abnormalities.

Management includes surgical treatment for Hirschsprung disease and supportive management of hearing impairment [2,10]. Clinical course and surgical planning are guided by the length of a ganglionic segment [10]. Early recognition of sensorineural deafness may play an important role in ensuring the development of speech and language [11]. In childhood, they are advised to avoid direct sunlight, using sunscreen with a high sun protection factor, use of specially tinted glasses or contact lenses thus reducing possible sensitivity to light. Genetic counseling is of immense benefit for affected individuals and their families [12].

CONCLUSION

The association of Waardenburg syndrome with Hirschsprung disease is rare. Mutation studies guide in the further characterization and counseling to the family. Prognosis is steered by the complications of Hirschsprung disease and size of aganglionic segment.

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