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A Term Newborn Who Has Abnormal Facies

JoDee M. Anderson, MD,¹ Gulzade Onk, MD,² Recep Polat, MD,² Ahmet Dursun, MD,³ Bahri Ermis, MD²

The Case

A term female presents with abnormal facies.



Figure 1. Photo of Baby.

Prenatal History

- 22-year-old gravida 1 para 0 Caucasian mother who has congenital deafness and the following phenotype
- Blood type O+, antibody screen negative, hepatitis B surface antigen negative, rubella immune, rapid plasma reagin nonreactive, group B *Streptococcus* screen negative

Birth History and Presentation

The infant was delivered by the vaginal route in vertex presentation. She made the transition to the extrauterine

¹Department of Pediatrics, Division of Neonatal-Perinatal Medicine at University of Texas Southwestern, Dallas.

²Department of Pediatrics, Division of Neonatology, Zonguldak Karaelmas University, School of Medicine, Zonguldak, Turkey.

³Department of Genetics, Zonguldak Karaelmas University, School of Medicine, Zonguldak, Turkey.

environment without difficulty, with Apgar scores of 9 at both 1 and 5 minutes. Her birthweight was 3.3kg, which was appropriate for gestational age.

Case Progression

Vital Signs

- Heart rate, 160 beats/min
- Respiratory rate, 48 breaths/min
- Blood pressure, 67/32 mm Hg
- Temperature, 98.1°F (36.7°C)

Physical Examination

- Lateral displacement of the medial canthi with short palpebral fissures, broad and high nasal bridge with hypoplastic alae nasi, white forelock view photo
- Lungs: Clear; equal breath sounds without retractions
- Cardiovascular Examination: Normal S1, S2; regular rhythm; no murmur; equal peripheral pulses
- Abdominal Examination: Soft and nontender; liver palpable 2 cm below the right costal margin; three vessels in the umbilical cord
- Genitourinary Examination: Normal female; patent anus
- Extremities: Normal; hips stable
- Neurologic Examination: Appropriate strength and tone
- Skin: No rashes or lesions; nonicteric

The infant failed the newborn hearing screen bilaterally.

Differential Diagnosis

Lateral Displacement of the Inner Canthi*

- Blepharophimosis Syndrome
 - Inner canthal fold, lateral displacement of inner canthi, ptosis
- Branchio-Oculo-Facial Syndrome
 - Branchial defects, lacrimal duct obstruction, pseudocleft of upper lip
- Carpenter Syndrome
 - Acrocephaly, polydactyly and syndactyly of feet, lateral displacement of inner canthi
- DiGeorge Sequence
 - Primary defect of the fourth branchial arch and the derivatives of the third and fourth pharyngeal pouches

- Dubowitz Syndrome
 - Peculiar facies, infantile eczema, small stature, mild microcephaly
- Fetal Valproate Syndrome
 - Epicanthal folds, telecanthus, cardiovascular defects, limb abnormalities, neural tube defects
- Freeman-Sheldon Syndrome
 - Masklike facies, pursed lips, hypoplastic alae nasi, talipes equinovarus
- Frontonasal Dysplasia Sequence
 - Primary defect in midfacial development, with incomplete anterior appositional alignment of eyes
- Mohr Syndrome
 - Cleft tongue, conductive hearing loss, partial reduplication of hallux
- Oral-Facial-Digital Syndrome
 - Oral frenula and clefts, hypoplasia of alae nasi, digital asymmetry
- Oromandibular-Limb Hypogenesis Spectrum
 - Hypoglossia-hypodactyly syndrome
- Waardenburg Syndrome
 - Lateral displacement of the medial canthi, partial albinism, deafness
- X-Linked Alpha-Thalassemia/Mental Retardation (ATR-X) Syndrome
 - Severe mental retardation, telecanthus, microcephaly, genital abnormalities

*Adapted from Jones KL, ed. Smith's *Recognizable Patterns of Human Malformation*. 5th ed. Philadelphia, Pa: WB Saunders Co; 1997.

Actual Diagnosis

Waardenburg Syndrome Type I

Diagnosed clinically according to the Waardenburg Consortium.

The Experts

History of Waardenburg Syndrome

Waardenburg syndrome (WS) is an autosomal dominant disorder characterized by varying degrees of hypopigmentation,



Figure 2. Photo of Mother's Eyes.

hearing loss, and defects in neural crest cell migration. The syndrome was named in 1951 by Petrus Johannes Waardenburg, a Dutch optometrist, who first defined the syndrome with six primary elements, including lateral displacement of the inner canthi with blepharophimosis, prominent broad nasal root, hypertrichosis of the medial eyebrows (synophrys), white forelock, heterochromia iridis, and deafness. The frequency of WS is estimated to be 1 in 200,000 in the general population of the Netherlands and 1 in 20,000 in Kenya. There is no race or sex predilection, despite these reported frequencies.

Definitions

Multiple terms are used to describe the abnormal ocular findings in WS. Lateral displacement of the inner canthi gives rise to short palpebral fissures, resulting in telecanthus. Telecanthus is defined as an increased distance between canthi and is synonymous with hypertelorism (increased distance between two organs). Dystopia refers to the abnormal position of part of an organ and frequently is used to describe the position of the eyes in WS (ie, dystopia canthorum). Blepharophimosis is defined as a decrease in the size of the palpebral aperture without fusion of the lid margins, which results in convergent strabismus.

Clinical Features

Infants who have WS can be identified soon after birth. Four types of WS have been described, and all forms demonstrate marked variability, even within families.

Type I WS is characterized by full symptomatology of the disease:

- Dystopia canthorum (99%)
- Hypoplasia of the nasal bone, short philtrum, repositioned maxilla
- Convergent strabismus, reduced visibility of the medial sclera

- Broad nasal root (80%)
- Heterochromia iridium (25%)
- Congenital deafness (25%)
- White forelock (45%)
- Cutaneous hypopigmentation

Type II WS is a heterogeneous group that does not include dystopia canthorum; white forelock and hypopigmentary skin lesions are also less common:

- Sensorineural hearing loss (77%)
- Heterochromia iridium (50%)

Type III WS is also referred to as Klein-Waardenburg syndrome. Type III WS is most similar to Type I (presenting with the full spectrum of symptomatology), but includes additional musculoskeletal anomalies:

- Aplasia of the first two ribs
- Cystic formation of the sacrum
- Cutaneous syndactyly
- Mental retardation
- Microcephaly

Type IV WS is also known as Shah-Waardenburg syndrome and describes the association of WS with congenital aganglionic megacolon (Hirschsprung disease).

Congenital deafness in WS can be bilateral or unilateral and severe or moderate. Patients who have hearing loss and WS have temporal bone anomalies, with 50% having enlargement of the vestibular aqueduct visible on computed tomography.

Cutaneous abnormalities include both hypopigmented lesions and hyperpigmented lesions and can resemble the lesions found in piebaldism, tuberous sclerosis, and neurofibromatosis.

Ocular color abnormalities of WS present in three patterns: heterochromia iridis, bilateral isohypochromia iridis (pale blue eyes), and hypopigmentation of the fundus.

Syndromes that have similar clinical features include Rozycki syndrome (deafness and viteligo), Fisch syndrome (congenital deafness and early graying of the hair), and Wolf syndrome (albinism and deafness).

Diagnosis

According to the Waardenburg Consortium, an individual can be diagnosed if two of the following major criteria or one major and two minor criteria are present:

Major Criteria

- Congenital sensorineural hearing loss
- White forelock
- Pigmentation abnormalities of the iris
- Affected relative
- Dystopia canthorum=W index greater than 1.95.

The measurements necessary to calculate the W index in mm are: inner canthal distance (a), interpupillary distance (b), and outer canthal distance (c)

$$\begin{aligned} \text{Calculate } X &= (a - 0.2119c + 3.909)/c \\ \text{Calculate } Y &= (2a - 0.2479b + 3.903)/b \\ \text{Calculate } W &= X + Y + a/b \end{aligned}$$

Minor Criteria

- Skin hypopigmentation
- Synophrys
- Broad/high nasal root
- Hypoplastic alae nasi
- Premature grey hair (before age 30 years)

WS is associated with neural crest-derived melanocyte deficiency caused by mutations in transcription factors. More than 90% of individuals who meet the clinical diagnostic criteria for WS Type I have mutations in the PAX3 gene. The PAX3 gene is located on chromosome 2 and controls some aspects of the development of the face and inner ear. Approximately 15% of individuals who have Type II WS are heterozygous for mutations in the microphthalmia-associated

transcription factor (MITF) gene. The MITF gene is found on chromosome 3 and is involved in the development of the ear. Type III WS is considered an extreme presentation of Type I, with some affected individuals being homozygous for the PAX3 gene mutation. Type IV WS can be caused by mutations in the genes for endothelin-3 or one of its receptors, EDNRB and EDN3 genes.

Key References

- Edery P, Attié T, Amiel J, et al. Mutation of the endothelin-3 gene in the Waardenburg-Hirschsprung disease (Shah-Waardenburg syndrome). *Nat Genet.* 1996;12(4):442-444
- Farrer LA, Grundfast KM, Amos J, et al. Waardenburg syndrome (WS) type I is caused by defects at multiple loci, one of which is near ALPP on chromosome 2: first report of the WS consortium. *Am J Hum Genet.* 1992;50(5):902-913
- Jones KL, ed. *Smith's Recognizable Patterns of Human Malformation*, 5th ed. Philadelphia, Pa: WB Saunders Co; 1997
- Potterf SB, Furumura M, Dunn KJ, Arnheiter H, Pavan WJ. Transcription factor hierarchy in Waardenburg syndrome: regulation of MITF expression by SOX10 and PAX3. *Hum Genet.* 2000;107(1):1-6
- Read AP, Newton VE. Waardenburg syndrome. *J Med Genet.* 1997;34(8):656-665
- Spritz RA. Piebaldism, Waardenburg syndrome, and related disorders of melanocyte development. *Semin Cutan Med Surg.* 1997;16(1):15-23
- Tekin M, Bodurtha JN, Nance WE, Pandya A. Waardenburg syndrome type 3 (Klein-Waardenburg syndrome) segregating with a heterozygous deletion in the paired box domain of PAX3: a simple variant or a true syndrome? *Clin Genet.* 2001;60(4):301-304

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