Picture Story

A case of type I Waardenburg syndrome

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Case report

A six year old boy presented with delay in acquiring language skills. Examination revealed heterochromia of both irides (Figure 1).

Mother’s eyes were similar in appearance. An audiological evaluation revealed moderate to severe sensory neural hearing loss. Similar ocular changes with hearing loss had been noted in a maternal uncle. All other family members appeared normal.

Figure 1

Discussion

Waardenburg syndrome (WS) is named after a Dutch ophthalmologist, who first described a patient with hearing loss, dystopia canthorum (i.e. lateral displacement of inner canthi of eyes) and retinal pigmentary changes in 1947. Since then 4 types have been described. The prevalence of WS is estimated at 1 per 42,000 individuals¹. Types 1 and 2 are believed to be equally common. This syndrome is considered to be responsible for 2-3% of cases of congenital deafness².

Both types 1 and 2 are autosomal dominantly inherited conditions with marked interfamilial and intrafamilial variability³. Both the auditory and pigmentary abnormalities can be explained by the failure of proper melanocyte differentiation. Melanocytes are required in the stria vascularis for normal cochlear function⁴. Most cases of WS1 are caused by mutations in the PAX3 gene located on Ch.2q35. PAX3 gene belongs to a family of paired-domain proteins that bind DNA and regulate gene expression⁵.

Evidence exists that the MITF gene (microphthalmia-associated transcription factor) transactivates the Tyrosine gene, which is involved in melanocyte differentiation⁶. A study in Watanabe in 1998 showed that PAX3 transactivates MITF-promotor. Mutations in the PAX3 gene, therefore, could affect regulation of the melanocyte differentiation. SOX10 gene interacts with PAX3 in regulating MITF gene and mutations of this gene have been implicated in the pathogenesis of WS⁴.

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The 4 types are differentiated as follows:3,8

- **Type 1**: hearing loss, dystopia canthorum and pigmentary abnormalities of the hair, skin and eyes.
- **Type 2**: all features of WS1 except dystopia canthorum.
- **Type 3**: features of type 1 & severe contractures (Klein-Waardenburg syndrome).
- **Type 4**: WS with associated Hirschprung disease (Waardenburg-Shah syndrome).

The following criteria have been proposed by the Waardenburg syndrome consortium to aid the diagnosis. The presence of 2 major or 1 major plus 2 minor criteria are considered to be diagnostic of WS.

**Major criteria**

Congenital sensory neural hearing loss  
Pigmentary disturbances of the iris  
Hair hypopigmentation  
Affected 1st degree relative  
Dystopia canthorum

**Minor criteria**

Congenital leucoderma  
Synophrys or medial eye brow flare  
Broad, high nasal root  
Hypoplasia of alae nasi  
Premature graying of hair

As our patient has pigmentary disturbances of the eyes in the presence of dystopia canthorum with an obvious family history, Waardenburg syndrome type 1 is most likely.

For confirmation of the diagnosis molecular testing in the form of mutation analysis of the PAX3 gene is available. Management issues would be genetic counseling and attending to the hearing impairment with a cochlear implant which is the only remedy. Prognostically, the affected are of normal cognition and their functions would depend on early detection of the hearing defect and initiation of stimulation. Mortality rates are comparable with the normal population.

References