Auditory pigmentary syndromes

Robbert JH Ensink reviews the most commonly encountered syndromes with (de)pigmentation disorders frequently accompanied by profound sensorineural hearing loss

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Hearing impairment and pigmentary disturbances are major features of a number of genetic disorders. There are a number of conditions in which deafness can be associated with hypo or hyperpigmentation of, mainly, skin and/or eyes. These clinical conditions are named auditory pigmentary syndromes. Waardenburg syndrome is the most common but rare clinical syndromes such as Tietz syndrome and Piebaldism also belong to this clinical spectrum. These clinical conditions are prevalent in sub-Saharan Africa and one will frequently encounter children with these syndromes when visiting deaf schools.

This article reviews the most commonly encountered syndromes with (de)pigmentation disorders frequently accompanied by profound sensorineural hearing loss. It will also briefly report on the latest studies performed in deaf schools with the aim to investigate the prevalence of genetic causes for profound hearing losses.

Waardenburg syndrome

Waardenburg syndrome is the most common depigmentation syndrome encountered in schools of the deaf. About 2-5% of the congenitally deaf people have Waardenburg syndrome. A study of pupils in schools the deaf by Sellars (1983) in South Africa revealed that about 3% of children have Waardenburg syndrome. In 10% of all children with Waardenburg syndrome a bilateral congenital hearing loss is present. A Nigerian study performed in a deaf-blind school suggested an incidence of 0.65% of Waardenburg syndrome in Western Africa. (Ahmed 2010). Another South African study based on 169 black pupils at the Pietermaritzburg school of the deaf using pure tone audiometry revealed in 10% a genetic non-syndromal cause; 2% of black pupils had Waardenburg syndrome (Clifton 1988).

The syndrome was first presented to the Dutch Ophthalmological Society in 1947 by Dr Petrus Waardenburg. A year before, a Swiss ophthalmologist Dr Klein, presented a Swiss deaf mute child with partial depigmentation of the hair and skin who had remarkably blue irides with malformations of the arms. Before the full account of the syndrome was published in 1951, already 100 cases had been identified in Dutch institutions of the deaf. Since 1951, the Waardenburg syndrome was used for this condition. Later, Waardenburg syndrome was classified into five different subtypes (WSI-WSV) based on the clinical findings. The so called Klein-Waardenburg is today categorized as Waardenburg syndrome type III which refers to the poor development of hands and/or arms of the upper limbs as well as hearing loss and pigmentation changes.

Clinical characteristics The major characteristics of Waardenburg syndrome are depigmentation of hair (in many a white forelock is present) and sometimes depigmentation of the skin around the head, face and body, with typically a profound perceptive hearing loss. This may be accompanied by a condition called dystopia canthorum (the eyes appear widely spaced due to a widened nasal root and lateral

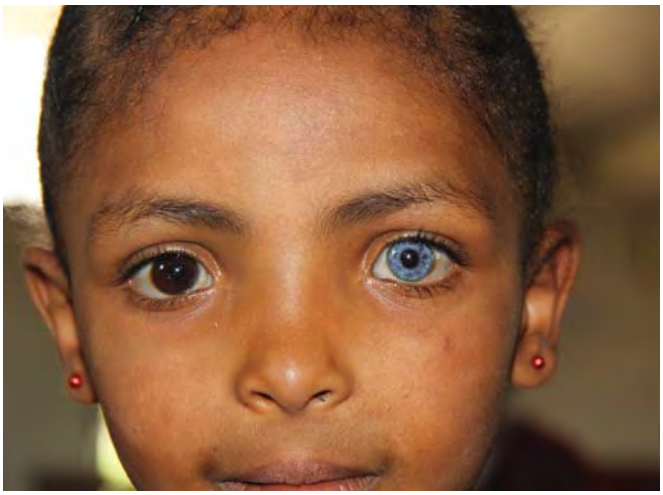


Figure 1: A newcomer in the school of the deaf in Maganissa deaf school, Addis Ababa, Ethiopia. Beside profound deafness, note the iris heterochromia

displacement of the inner corner/canthus of each eye) sometimes referred to as a telecanthus. Dystopia canthorum is a characteristic finding in Waardenburg syndrome type I but telecanthus is not a feature of type II. Types I and II are the most common forms of Waardenburg syndrome, comprising respectively half and a third of cases.

The most striking clinical feature is the pigmentary disturbances of the irides; several variants can occur ranging from heterochromia (eyes of different color) to iris bicolor (segments of different color blue and brown in one or both eyes) and sapphire blue irides. (Figure 1) The literature also has described many clinical variations of the syndrome including Hirschsprung disease (a bowel disorder) as well as associations with neurofibromatosis (a neurocutaneous syndrome). However, there is a school of thought that these clinical entities are unlikely to be part of this syndrome and are probably more coincidental.

Genetics The hereditary trait in Waardenburg syndrome is mainly autosomal dominant. In this trait, 50% of the offspring inherit the affected gene from a mother or father with clinical similarities of the syndrome. Although rare, some traits seem to occur as a spontaneous mutation, meaning there is no family history.

The clinical expression of the gene (phenotype) varies considerably and makes accurate diagnosis in mildly affected offspring difficult. Today, however, due to gene linkage studies from the past in families with audio-pigmentary syndromes, a diagnosis can be confirmed by identifying the so called PAX3 genes mutations (type I and type III) and also mutations in a variety of genes in type II with the MITF gene mutation as the most important.

All these genes play an important role in the formation of neural and skin tissue which form together during embryogenesis. Regarding the cochlea, these genes are important in formation of neural cochlear cells and especially the stria vascularis.

Also, in rare syndromes like Piebaldism (larger hypopigmented, immune-mediated patchy skin lesions) and Tietz syndrome (full manifestation of clinical features in the offspring), skin lesions are present as well as profound sensorineural hearing loss, and they have their origin also in altered cells originating from altered development of neural crest cells due to different mutations in PAX3 and MITF genes that result in mutated, cell lineages of peripheral neuronal nerve cells and skin cells (melanocytes).

Oculo-Cutaneus Albinism It is not only Waardenburg syndrome that is associated with pigmentary abnormalities. In Tanzania, approximately 10% of school children with albinism had a hearing loss. A study on 64 people with albinism in the Moshi district showed that about 52% of individuals had unilateral or bilateral losses in excess of 40dB. The pattern that was most commonly found consisted of air conduction losses in mainly the lower frequencies (Jiwaji, 2009).

There are more syndromes that have cutaneous anomalies but usually not with profound hearing losses. In neurofibromatosis type I, café-au-lait macules and cutaneous neurofibromata are present although they are mostly absent in type II. In type II a clear autosomal dominant pattern is present and bilateral neuromata of the acoustic nerve are frequently present. Usher syndrome is not frequently seen in deaf schools in Sub Saharan Africa. It is an autosomal recessive disorder meaning the affected gene is transferred from healthy parents to their offspring with a risk factor of 25%. For the African continent, prevalence figures are only available for South Africa and they are around 0.27% of the deaf cohort.

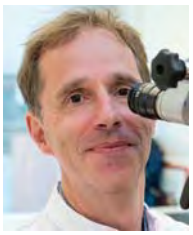
Studies on hereditary causes in the schools of the deaf

Several studies have investigated the prevalence of hereditary causes in deaf schools in Africa. Most studies were carried out in the early 80s in South Africa. They have been reported above in detail already. (Sellars, 1983; Beighton 1983,1987). McPherson (1985) reported a prevalence of 8.1% in a study of genetic causes of profound hearing loss in the Gambia. This study reported on a prevalence of 8.1% of genetic causes found in profound hearing losses.

Surprisingly, with growing availability of gene linkage, only two studies were published on the etiology of deafness in the schools for the deaf in Africa after 2000. To date, the biggest cohort studied (Wonkam, 2015) was in Cameroon. In 2013, a register was made of 582 individuals recruited from schools for the deaf (n=522) and profoundly hearing-impaired people (>80 dB) from several ENT practices (n=60). Pure sensorineural hearing loss was present in 85%. Acquired causes were mainly meningitis (34%). Genetic causes were present in 14% and mainly non-syndromic autosomal recessive (86%). This is in accordance with the assumption that around ¾ of all hereditary losses are non-syndromal and probably due to autosomal recessive inheritance. Of all the syndromic cases in this study about half were Waardenburg syndrome. However, still one third of all cases were "cryptogenic". A possible explanation suggested by the authors is still the lack of sufficient diagnostic tools. Ogunkeyede (2017) described etiologies in 155 Nigerian children that attended the schools for the deaf. In 56%, a febrile illness was the reason; in 5%, hereditary causes were present; in 5% a head trauma was reported and, in 10 %, unknown reasons were present. In an additional 10%, the reasons for hearing loss was attributed to a "spiritual attack".

Conclusion

On regular visits to deaf schools one might encounter children with profound deafness and syndromal characteristics of Waardenburg syndrome. This syndrome is the most frequent syndromal cause of hearing loss in children that attend the school for the deaf. There are still many unknown causes for profound hearing loss in children that attend the school of the deaf. It is considered that, in these cryptogenic causes, non-syndromal autosomal recessive inheritance patterns play a major role. With increasing advances and decreasing costs of genetic testing, clinicians are likely to understand the aetiology of hearing loss more accurately in the future.



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