FAMILIAL DEAFNESS AND IRIS ATROPHY - REPORT FROM NIGERIA

[1]Yusuf T., [1]Babarinde J.O., [2]Olajide I., [1]Owolabi T., [2]Popoola K.O., [1]Musa I., [3]Adedeji W.A., [4]Vangerwua B., [5]Abraham T.F., [2]Fasina O., [1]Lasisi O.A.

[1]Department of Otorhinolaryngology, University College Hospital, Ibadan, Oyo State, Nigeria, [2]Department of Ophthalmology, University College Hospital, Ibadan, Oyo State, Nigeria, [3]Department of Pharmacology, College of Medicine, University of Ibadan/University College Hospital, Ibadan Departments of [4]Physiology and [5]Audiology, Federal University of Health Sciences, IIa-Orangun

ABSTRACT

Waardenburg's syndrome (WS) is an uncommon autosomal dominant or recessive disorder. The complete syndrome is rare and variation in the clinical presentation of WS is due to the expression of different genes.
Herein we report a familial case of a man and his children a boy and a girl, who have iris atrophy with deafness. The diagnosis of Waardenburg's syndrome was made because three major diagnostic criteria were identified in them.

Keywords; *Waardenburg syndrome, sensorineural hearing loss, autosomal dominant, iris atrophy, gene*

INTRODUCTION

Waardenburg syndrome (WS) is a rare inherited disorder of neural crest cell development.[1] It usually shows an autosomal dominant mode of inheritance, but autosomal recessive inheritance patterns are observed in some subtypes.[2] The highest reported incidence of WS is among Kenyan Africans.[1] The prevalence varies from 1:20000 to 1:40000.[3] WS accounts for between 2% and 5% of cases of congenital deafness.[4]
The syndrome, as it was described by Waardenburg (1951), consists essentially of the following components:[2,5]

1. Dystopia Canthi-Telecanthus, an increase in the distance between the medial canthi beyond the normal range
2. Hyperplasia Supercilii Medialis et Radicis Nasi-This has been described by Waardenburg as characterized by a high nose-bridge with hypertrichosis of the eyebrows which tend to join in the mid-line (synophrys).
3. Heterochromia Iridum Totalissive Partialis. Hypopigmentation and hypoplasia of the iris stroma may be present in one or both eyes.
4. Surditas Congenita. The deafness found in this syndrome is perceptive and belongs to one of two distinct types. "Type 1" shows almost total deafness with a little residual hearing for the lower range of frequencies, and "Type 2" a moderate degree of deafness with uniform hearing loss for the lower and middle ranges of notes with improvement for the higher notes.
5. Albinismus Circumscriptus-A median white fore-lock may vary in intensity from a few white hairs to the obvious picture found in some cases.
   The diagnostic criteria consist of major and minor criteria[2]; major include sensorineural hearing loss, pigmentary abnormality in the iris, segmental, partial, or complete heterochromia iridis, isohypochromia, fore hair's achromia, dystopia canthorum and affected first degree relative. Minor criteria include congenital leukoderma, synophrys, broad and high nasal root, hypoplasia of nasal alae, and premature greying of hairThere are four different types of Waardenburg syndrome based on clinical characteristics, including WS1, WS2, WS3, and WS4.[6] Diagnosis of WS1 needs either two characteristics from major criteria or one major characteristic with two minor characteristics. In WS2
dystopia canthorum is absent while WS3 has the same features as that of WS1 but the only difference is the presence of upper limb malformations. WS4 is easy to diagnose as it is always linked with Hirschsprung disease.[6,7]

Correspondence:
Yusuf T.
Department of Otorhinolaryngology, University College Hospital, Ibadan, Oyo State, Nigeria
Email: drtjry@gmail.com

PATIENTS AND METHODS

This is a report of a rare case of deafness with associated iris atrophy in a family. The case was encountered in a survey of deafness currently going on in Nigeria and the informed consent of the subject was obtained. This involves a 33-year-old father and his children (a male 14-year-old and a female 11-year-old) Fig. 1, 2 and 3. The iris atrophy is a feature that classically defines the genetic link between them and the syndrome. The pure tone audiometry of the participant as displaced in Fig 4, show that the severe sensorineural hearing loss is common to three of them. So also, the family pedigree (Fig 5), how the syndrome was inherited in the family.

Figure 1: 33-year-old father

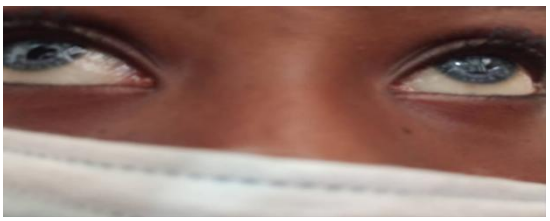

Figure 2: 14-year-old son

Figure 3: 11-year-old daughter

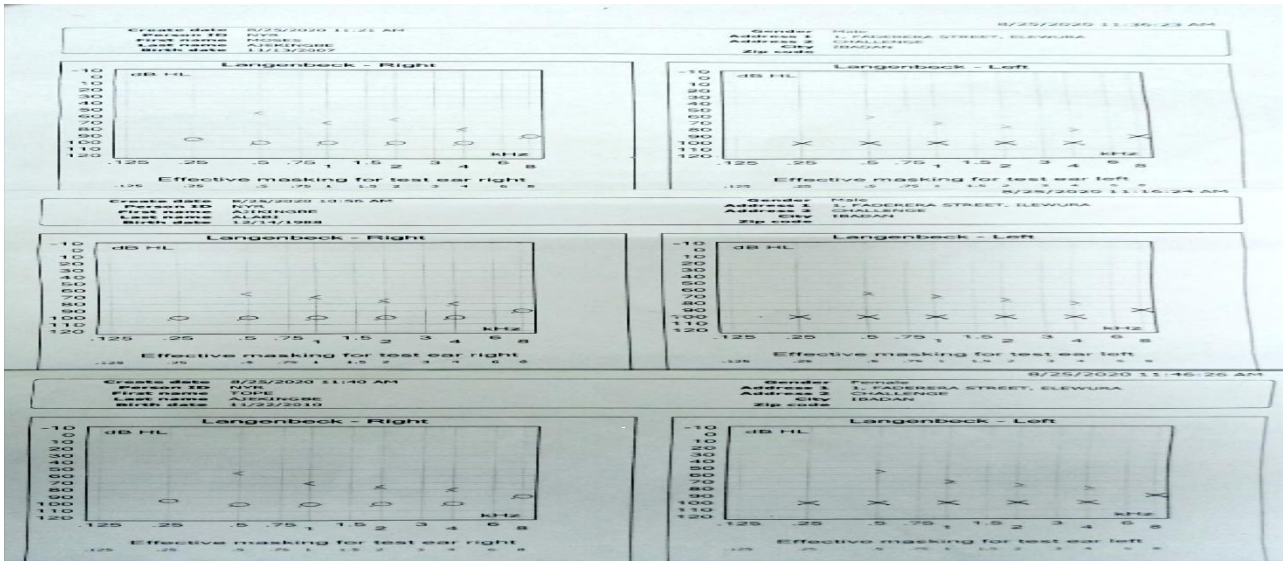

Figure 4: Pure tone audiogram of the man and his children

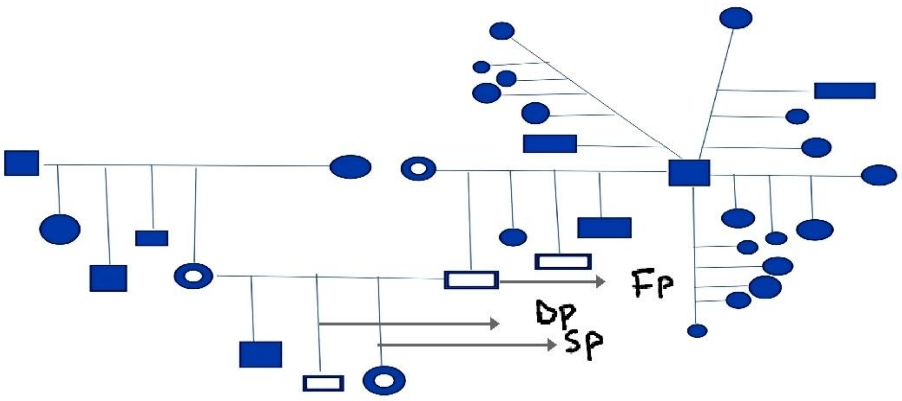

Figure 5: the family pedigree

Keys
Oval (shaded)
Rectangle (shade): male
Rectangle: male (deaf)
Oval circle: female (deaf)
FP-father
SP: son
DP: daughter

DISCUSSION

Multiple genes are involved in the WS like the PAX3 gene (paired-box-gene-3) shows a mutation in the patients of WS1 and WS3 while mutation of the MITF (microphthalmia-associated-transcription factor) gene is involved in WS2. In WS4 cases, multiple gene mutations are involved including either EDN3 (endothelin-3) or EDNRB (endothelin receptor type-B) or SOX10 (SRY-sex determining region Y-box-10) gene.[8] In most cases, Waardenburg syndrome type I (WS1) and type II (WS2) are inherited as autosomal dominant traits with variable penetrance and expressivity. Some cases of Waardenburg syndrome type III (WS3) and type IV (WS4) appear to have an autosomal recessive pattern of inheritance.[9,10]
Since both the iris stroma and inner ear are derived from neural crest cells, the changes may represent a progressive abiotrophic degeneration of neural crest derivatives.11 Pax genes play an important role in the migration and differentiation of neural crest cells, while mutations of Pax-3 and Pax-6 are now known to be responsible for the abnormalities of neural-crest-derived tissues that form part of Waardenburg's syndrome and aniridia respectively.[12,23 14]
This case was diagnosed as Waardenburg's syndrome (WS) based on three major criteria including sensorineural hearing loss, pigmentary abnormality in the iris, and affected first-degree relative. About 25% of WS cases reported partial or complete heterochromia iridis5,[6,7,15] and the current case also favoured this finding. Considering sensorineural hearing loss, about 67% of WS1 cases while 87% of WS2 cases had reported congenital deafness7 this was also found in this familial case.
The degree of hearing loss found in these people was severe to profound sensorineural hearing loss which is almost in agreement with what is associated with WS1.5WS1 is an autosomal dominant disorder that shows the presence of the affected gene in parents but rarely in a few of the cases there is de novo mutation as the parents are not affected.[16] In the current case we couldn't perform gene sequencing but it looks like a familial case or an autosomal dominant disorder since it is found in the father and his children.

CONCLUSION

Waardenburg's syndrome is rarely reported in our population so it is important to report this identified familial case. Though this was an incidental finding in a survey of deafness in Nigerian communities, gene sequencing among the identified cases would better enhance the proof of genetic bases of the syndrome.
There is also a need for parent's education regarding this genetic disorder.

Consent and ethical approval
As per international standard, parent consent of the patient and ethical approval has been collected and preserved by the authors.
Competing interests

The authors have declared that no competing interests exist.

REFERENCES

1. Rawlani S.M, RamtakeR, A. DhabardeA., Rawlani S.S.Waardenburg syndrome: A rare case. Oman journal of ophthalmology. 2018: 11(2); 158-160
2. Waardenburg PJ: A new syndrome combining developmental anomalies of the eyelids, eyebrows, and nose root with pigmentary defects of the iris and head hair and with congenital deafness. Am J Hum Genet. 1951 3:195-255
3. Pingault V, Ente D, Dastot-Le Moal F, Goossens M, Marlin S, Bondurand N, et al. Review and update of mutations causing Waardenburg syndrome. Hum Mutat 2010; 31:391-406.
4. Nayak CS, Isaacson G. Worldwide distribution of Waardenburg syndrome. Ann Otol Rhinol Laryngol 2003; 112:817-20.
5. J S Cant and A J Martin. Waardenburg's syndrome. Report of a family. Br J Ophthalmol. 1967; 51: 755-759
6. Sadiq S., Langah A., Ali Akbar Siyal AA, Ali N U. Waardenburg Syndrome: A Case Report. Asian Journal of Pediatric Research. 2019; 2(4): 1-4
7. Tagra S, Talwar AK, Walia RLS, Sidhu P. Waardenburg syndrome. Indian Journal of Dermatology, Venereology and Leprology. 2006; 72(4): 1-4
8. Yang S-Z, Cao J-y, Zhang R-n, Liu L-x, Xin L, Zhang X, et al, Nonsense mutations in the PAX3 gene cause Waardenburg syndrome type 1 in two Chinese patients. Chinese Medical Journal. 2007; 120 (1): 46-49
9. Dourmishev AL, Dourmishev LA, Schwartz RA, Janniger CK. Waardenburg syndrome. Int J Dermatol 1999; 38:656-63
10. Farrer LA, Grundfast KM, Amos J, Arnos KS, Asher JH Jr., Beighton P, 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. 50:902-13
11. Mills PV. Iridoschisis. Br J OphthalmoI1967; 51:158-64.
12. Hogan BLM, Horsburgh G, Cohen J, Hetherington CM, Fisher G, Lyon MF. Small eyes (Sey): a homozygous lethal mutation on chromosome 2 which affects the differentiation of both lens and nasal placodes in the mouse. J Embryol Exp Morphol 1986; 97:95-110.
13. Baldwin CT, Hoth CF, Amos DA, da Silva EO, Milunsky A. An exonic mutation in the HuP2 paired domain gene causes Waardenburg's syndrome. Nature 1992; 355:637-8.
14. Ton CCT, Hirvonen H, Miwa H, Well MM, Monaghan P, Jordan T, et al. Positional cloning, and characterisation of a paired box- and homeobox-containing gene from the aniridia region. Cell 1991; 67:1059-74.
15. Demirci GT, Atıs G, Altunay IK. Waardenburg Syndrome type 1: A case report. Dermatology Online Journal. 2011; 17(11).
16. Pagon RA. GeneReviews: University of Washington; 1993