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Case Report

Waardenburg syndrome: a rare genetic disorder in four generations of a family

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ABSTRACT

Waardenburg Syndrome (WS) is a rare autosomal dominant disorder manifesting with sensorineural deafness, pigmentation defects of the skin, hair and iris and various defects of neural crest derived tissues. A primigravida mother delivered a full term, appropriate for gestational age, 2530 gm female child, by emergency LSCS. Baby was admitted in the NICU in view of features suggestive of Waardenburg syndrome, like white forelock of hair, broad nasal root and hypopigmented patches on the skin for further work up and management. Several members in the family were affected in the last 4 consecutive generations. Our baby was feeding well and discharged home after an uneventful hospital stay. Early diagnosis, detection of findings of hearing loss and the characteristic ophthalmic findings as well as regular follow up is necessary to enable the patient to lead a better quality of life.

Keywords: Baby, Blue iris, Sensorineural hearing loss, Waardenburg syndrome, White forelock

INTRODUCTION

Waardenburg syndrome is a rare inherited disorder characterized by deafness in association with pigmentary anomalies and various defects of neural crest-derived tissues. Globally the incidence of WS is estimated to be approximately 2/100000 worldwide.[1] It is an autosomal dominant disorder manifesting with sensorineural deafness, pigmentation defects of the skin, hair and iris and various defects of neural crest-derived tissues.[2] WS is classified into 4 subtypes, WS type1, WS type 2, WS type 3 and WS type 4, based on the clinical presentation.[3] A thorough clinical examination, identification of characteristic clinical features, a complete family history and specialized investigations are needed for the diagnosis of WS.[1] WS may be diagnosed at any time from birth to childhood, or even later in life.[1] We present one such rare undiagnosed case of Waardenburg syndrome with family history of clinical features of WS.

CASE REPORT

A primigravida mother delivered a full term, appropriate for gestational age, 2530 gm female child, by emergency LSCS in view of pain in abdomen with severe anemia. Baby had normal APGAR score of 8, 9, 9 at 1,5 and 10 minutes respectively. The vital parameters of the baby were stable after birth. Baby was admitted in the NICU in view of syndromic features noticed at birth for further work up and management. On general examination the child had a white forelock of hair anteriorly on the scalp, broad nasal root with normal alae nasi (Figure1). Both the irides were black in colour without any evidence of dystopia canthorum (lateral displacement of inner canthi). The Waardenburg (W) index was 1.68 in our baby. (W

index larger than 1.95 is considered significant for dystopia canthorum). Our baby also had symmetrically placed hypopigmented patches (mirror image of each other) of equal size (each measuring 9cm x 3cm) and shape, dorsally, over both knee joints, along with a single hypopigmented oval patch measuring 3cm x 2 cm on the left side of the umbilicus (Figure 1).

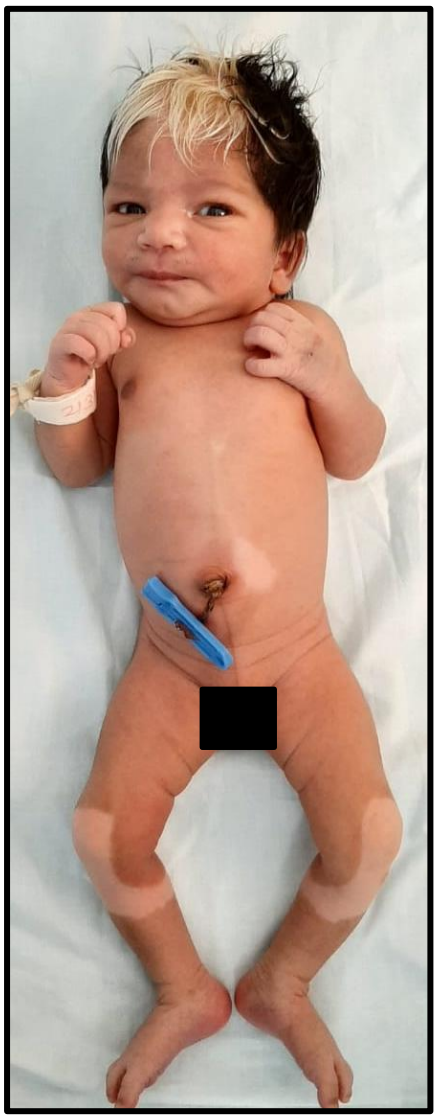

Figure 1: Clinical findings in skin and hair of WS baby.

On enquiry it was noticed that similar skin lesions (white forelock of hair and hypopigmented skin patches) were found in 8 members (mother, mother's sister and her son, maternal uncle, maternal grandmother and her sister and also the grandmother's father who has expired) in 4 consecutive generations (Figure 2,3,4). None of the family members had hearing abnormality or ophthalmic problems. Our baby is born of a 3rd degree consanguineous marriage. Routine investigations of the baby including complete blood count (CBC), X-ray chest and abdomen were normal.

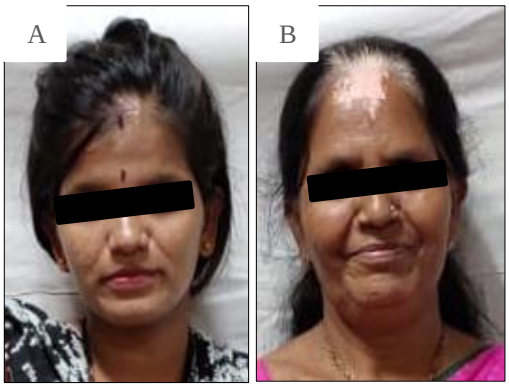

Figure 2: Clinical findings in skin and hair of scalp mother (A)and maternal grandmother (B) with WS.

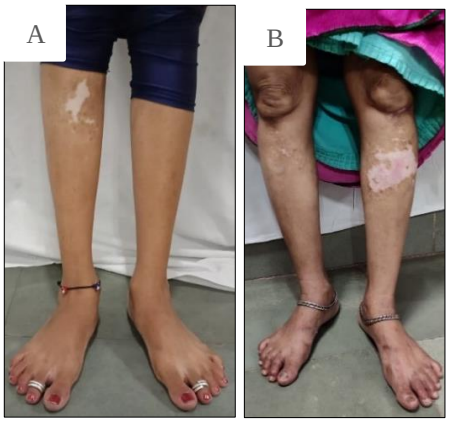

Figure 3: Clinical findings in skin of legs mother (A) and maternal grandmother (B) with WS.

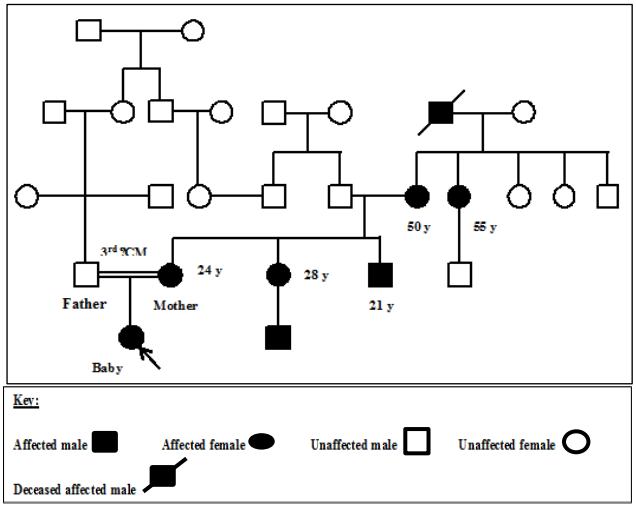

Figure 4: Pedigree chart of family with WS.

Ophthalmologic consultation was normal without any heterochromia. ENT (ear, nose, throat) consultation including otoacoustic emissions (OAEs) and auditory brainstem response test (ABR) were normal. Dermatology consultation confirmed our diagnosis of WS. There were no symptoms of any musculoskeletal or intestinal system

involvement noticed during the hospital stay in NICU. Our baby fulfilled 2 major and 2 minor of the Waardenburg criteria and was diagnosed as WS, especially, type II in view of absence of dystopia canthorum. The family was counselled and genetic work up was advised to the family but could not be done due to financial constraints. The child was feeding well, gaining weight adequately and was subsequently discharged. On follow up, presently the child is 45 days old and is growing well without any additional complications (Figure 5).

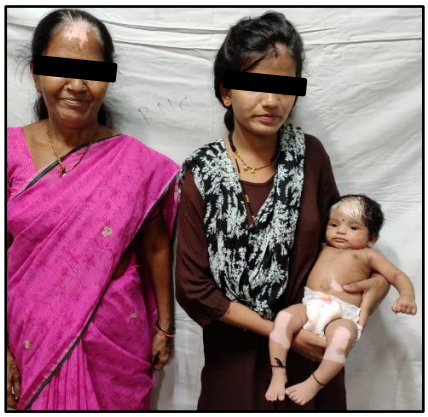

Figure 5: Clinical photograph of WS baby, mother (A) and maternal grandmother (B) on follow up.

DISCUSSION

WS is a rare autosomal dominant disorder manifesting with sensorineural deafness, pigmentation defects of the skin, hair and iris and various defects of neural crest derived tissues.[4] This genetically heterogeneous disease accounts for 2 % of the congenitally deaf population.[1,2,4] WS is inherited in an autosomal dominant manner, with the majority of the probands being affected parents. Minority who do not have an affected parent may be presumed to be de novo cases.[1] The autosomal dominant nature of inheritance is responsible for many members of a family, including both males and females, being simultaneously affected, as in our case, where the clinical features of WS were prevalent in 8 members spread over 4 consecutive generations. WS is named after a Dutch ophthalmologist, P. J. Waardenburg, who described a syndrome comprising of six distinctive features: lateral displacement of the medial canthi and lacrimal punctae, broad and high nasal root, hypertrichosis of medial part of the eyebrows, partial or total heterochromia iridis, white forelock, and congenital deaf mutism.[1-4]

The etiopathogenesis of WS is lies in the mutations in the EDN3, EDNRB, MITF, PAX3, SNAI2, and SOX10 genes which disrupt the normal development of melanocytes resulting in their physical absence from the skin, hair, eyes, or the striavascularis of the cochlea.[2] Melanin is produced by melanocytes contributing to the skin, hair, and eye color as well as the normal function of the inner ear. These mutations are the root cause of these auditory-pigmentary syndromes, leading to abnormal pigmentation of the skin, hair, eyes and hearing problems.[2] WS is classified into four clinical types, namely Type 1, 2, 3 and 4 Waardenburg syndrome based on the clinical features and the genes involved.[2] Mutations in the PAX3 gene is responsible for WS types 1 and 3. Similarly type 2 WS is caused by mutations in MITF and SNAI2 genes. Mutations in the SOX10, EDN3, or EDNRB genes cause WS type 4.[1-3]

Table 1: Diagnostic criteria proposed by the Waardenburg Consortium.

Major criteria	Minor criteria
1. Sensory neural hearing loss (SNHL) 2. Iris pigmentary abnormality a) Two eyes of different color. b) Iris bicolour/segmental heterochromia-an eye with two different colours. c) Characteristic brilliant blue iris. 3. Hair hypopigmentation a) White forelock. b) Body hair: white hairs within eyebrow, eyelashes, or at other sites on the body. 4. Dystopia canthorum: (W index) >1.95 5. First-degree relative diagnosed with WS	1. Several areas of hypopigmented skin 2. Synophrys or medical eyebrow flare 3. Broad high nasal root 4. Hypoplasia of alae nasi 5. Premature greying of the hair

Presence of two major or one major plus two minor criteria are required for the diagnosis of W

The diagnostic Waardenburg consortium criteria (Table 1) states that a person must have two major or one major plus two minor criteria to be diagnosed as WS.[2] The major criteria include congenital SNHL which is usually nonprogressive, varying from slight to profound, hair hypopigmentation (either a white forelock of scalp hair or white hairs within eyebrow, eyelashes, or at other sites on the body), pigmentary disturbance of the iris, dystopia

canthorum (lateral displacement of the inner eye corners with reduction of visible sclera medially), and first-degree relatives diagnosed with WS.[1-4] Minor criteria include Congenital hypopigmentation of the skin, medial eyebrow flare (synophrys), hypoplastic alae nasi, prominent broad nasal root, and early graying of hair before the age of 30.[1] Our baby thus fulfilled 3 major and 2 minor of these criteria qualifying for WS.[1-4]

The phenotypic distinguishing characters of each type of WS are as follows: the most common types are type 1 and type 2 which are often similar in their clinical features.[1] WS type I, is characterized by evidence of dystopia canthorum and the full symptomatology of the disease including a narrow nose (hypoplastic lower lateral cartilages, usually resulting in narrow lower third of the nose), marked hypoplasia of the nasal bone, short philtrum with short and retropositioned maxilla.[2] Iris pigmentary abnormality including either two eyes of different colour, or iris bicolor/segmental heterochromia (an eye with two different colors)/ or characteristic brilliant blue (sapphire) iris (alternatively described as ‘‘Waardenburg blue eye,’’ sky-blue eyes, or hypopigmented iris) were absent in our baby.[2] The hypoplastic blue irides feature is seen in only 15-18% of all WS patients.[5] Clinically, type 1 (WS1, MIM193500) and type 2 (WS2; MIM 193510) can be distinguished only by dystopia canthorum, which is characteristic of WS type 1 (WS1) and absent in WS type 2 (WS2) as in our baby.[1,3] SNHL may be either unilateral or bilateral and more often associated with WS2 than WS1.[1] Sensorineural hearing loss (77%) and heterochromia iridium (47%) are the 2 most important diagnostic indicators of WS type II.[2] Type 3 (WS3, Klein-Waardenburg syndrome, MIM 148820) which has the same symptoms as WS1, along with additional musculoskeletal limb abnormalities manifests with a cleft palate, musculoskeletal system hypoplasia and syndactly.[1,3] WS3 is the rarest form of WS.[3] Type 4 (WS4, Shah-Waardenburg syndrome, MIM 277580) is associated with Hirschsprung disease and its most defining feature is the aganglionic megacolon.[1,3] WS3 and WS4 are rare compared to WS1 and WS2, with WS3 being the rarest of all 4 types.[2,3] WS4 can be autosomal dominant or at times autosomal recessive.[6] White forelock present at birth may disappear later in life, with either reappearance in teens or adulthood, or may appear for the first time at any age.[2] Skin hypopigmentation occurs in 8.3-50% of WS patients with piebaldism.[4] Premature graying of scalp hair, eye brows, cilia or body hair has been reported to occur in 7% cases.[7]

The close differentials considered in our WS baby were piebaldism and albinism which have certain features similar to WS like, the age of presentation since birth and presence of hypopigmented skin lesions; however they differ in their genetic mutations.[8] The skin lesions in WS are distributed on face, neck, trunk, involving the dorsal limbs which was seen characteristically in our baby, whereas in piebaldism they are distributed on central forehead with white forelock, mid-trunk sparing dorsal spine, mid-arms/legs sparing hands/feet.[8] Other special differentiating features of piebaldism are hyperpigmented macules in the white macules, which were absent in our baby and hence piebaldism was ruled out in our baby. Albinism has a generalised distribution of skin lesions and may develop nevi, freckles, lentigenes which was absent in our baby.[8] Characteristic differentiating points for WS are white forelock with eyebrow hyperplasia along with other extracutaneous characters like heterochromicirides, broad nasal root, deafness whereas predominantly only poliosis is seen in piebaldism and only white hair in albinism. The extracutaneous characters seen in albinism are nystagmus, iris translucency, foveal hypoplasia, reduced visual acuity, which were absent in our baby.[8] The major diagnostic clues of WS in our baby are: a positive family history with a cluster or partial cluster of typical features in a patient with poliosis and deafness. In albinism the major diagnostic clues are characteristic changes in the development and function of eye and optic nerve with diffuse hypopigmentation along with autosomal recessive inheritance pattern which was not seen in our baby.[8]

Out of all morbidities seen in WS, the most common and significant serious morbidity is congenital deafness which warrants the artificial cochlear implantation at the earliest, to ultimately improve the speech of the patient.[2-4,6,7] It is necessary that family members make use of communication skills by receiving specialized training for impaired hearing in the family. A combination of dermabrasion and grafting of pigmented skin into depigmented areas, with or without phototherapy can be tried for selected cases with skin lesions.[8] A multidisciplinary team of medical professionals including an otolaryngologist, audiologist, speech therapist, geneticist, genetic counsellor, ophthalmologist, dermatologist, gastroenterologist and dentist is required for the optimal management of the WS patients. Genetic counselling is a must to confirm the diagnosis as well as the type of WS.[4]

CONCLUSION

All the clinical symptoms of WS1 and WS2, except sensorineural hearing loss, are essentially benign and cosmetic in nature and do not necessitate active intervention. Sensorineural deafness, musculo-skeletal abnormalities, and Hirschsprung disease are some of the serious morbidities associated with WS which significantly deteriorate the patient’s quality of life. The characteristic cutaneous features are a clue to the early diagnosis of WS for initiation of early treatment, social and vocational training and rehabilitation.

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