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Case Report

Waardenburg syndrome: A case series

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Abstract Waardenburg syndrome is a rare autosomal disorder with heterogeneous manifestations including sensorineural deafness, piebaldism, heterochromic irides, synophrys and dystopia canthorum. We report this case for its rarity and presence of freckles, a finding which has not been reported in association with WS in this part of world so far.

Key words
Waardenburg syndrome, piebaldism, dystopia canthorum, synophrys.

Introduction

Waardenburg syndrome (WS) was first described by and named after P.J. Waardenburg in 1951.[1] It includes spectrum of manifestations all caused by congenital neural crest cell abnormalities. This has an estimated incidence of 1 in 20-40000. Patients present with congenital sensorineural deafness, heterochromic irides, skin and hair hypopigmentation and various eye abnormalities.[2] We report a series of four patients having specific features of this syndrome.

Case Reports

First case was a 14-year-old boy who presented in dermatology outpatient clinic with hypopigmented patches over abdomen, both hands and right arm since birth along with grey hair at frontal scalp. He was born of consanguineous parents at full term by normal vaginal delivery. His developmental history was also normal except that he had congenital deafness and mutism. Physical examination revealed broad nasal root, synophrys, dystopia canthorum, heterochromic irides, hypoplastic nasal alae and multiple freckles over face. Visual acuity was normal in both eyes (**Figure 1** and **2**).

Second case was elder sister of above-mentioned patient, a 23-year-old girl having small depigmentary macules over hands since birth. She also had congenital deaf-mutism, broad nasal root, increased intercanthal distance, synophrys, bilateral blue eyes, white hair over scalp (dyed with henna) and freckles over face (**Figure 3** and **4**).

Our third patient was maternal cousin of above two patients, 18-year-old female with bilateral blue eyes, medial eyebrows, broad nasal root, piebald like skin patches over face, upper and lower limbs. She had white forelock (not appreciable due to hair dye) and depigmented eyebrows and eyelashes. She was also deaf and mute since birth and had multiple hyperpigmented macules over face (**Figure 5** and **6**).

Fourth patient was a 7-year-old boy, brother of case 3 having bilateral blue eyes. This patient

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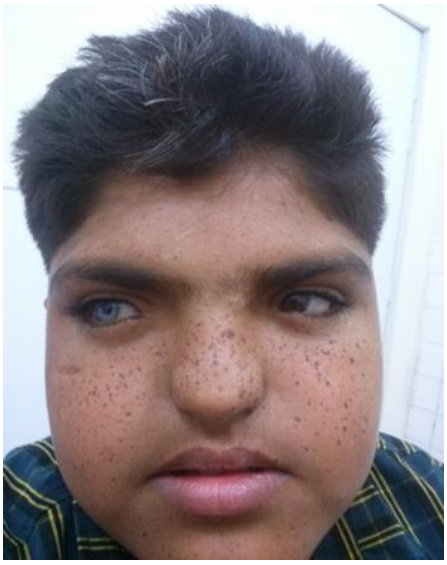

Figure 1 Heterochromic irides, broad nasal root, dystopia canthorum, synophrys, hypoplastic ala nasi, freckles and white forelock

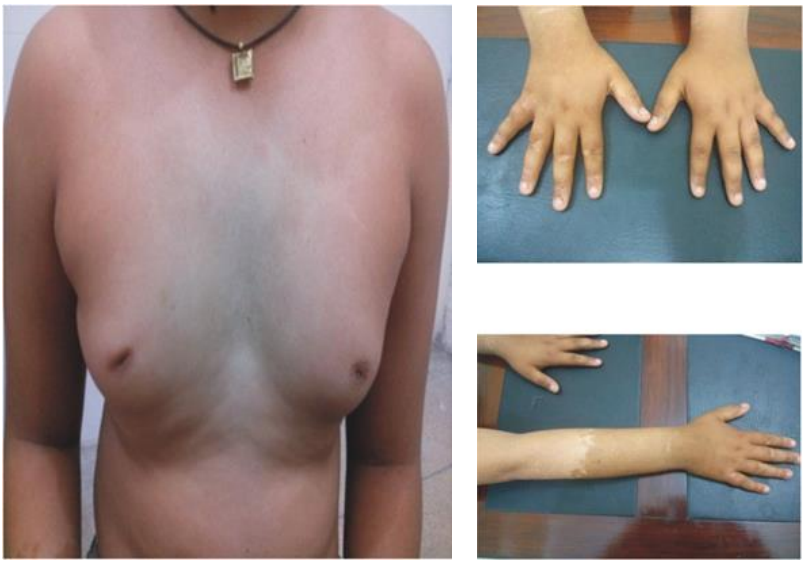

Figure 2 Hypopigmented macules and patches over abdomen and upper limb

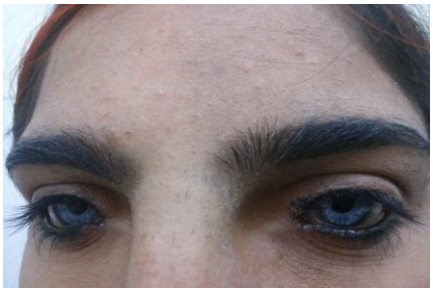

Figure 3 Blue eyes, broad nasal root, white hair on frontal scalp(dyed), synophrys (not appreciable due to plucking), dystopia canthorum

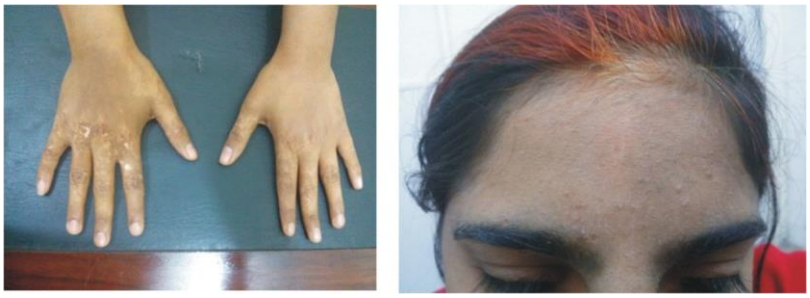

Figure 4 Vitiligo like macules over hands, white forelock (dyed with henna)

Figure 5 Blue eyes, broad nasal root, dystopia canthorum, synophrys, and piebald like patch over right nasolabial fold and lentigines and white eyebrows and eyelashes.

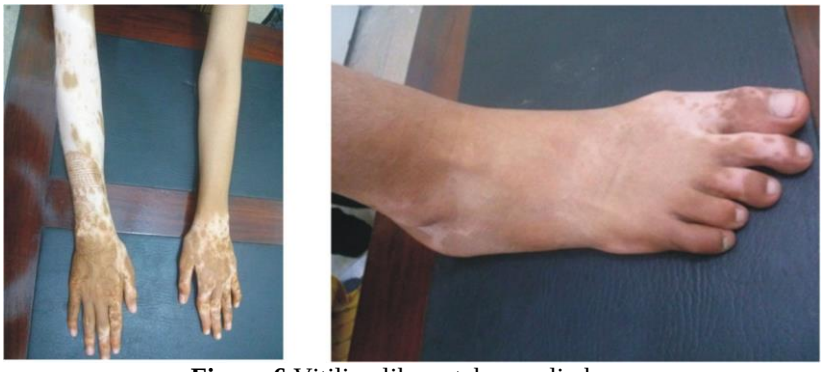

Figure 6 Vitiligo like patches on limbs.

was also suffering from deafness since birth. Additional features included dystopia canthorum, synophrys, broad nasal root, and vitiligo like patches over limbs, brown macules over face and hypoplastic nasal alae (**Figure 7** and **8**).

None of our patients had musculoskeletal abnormalities, gastrointestinal manifestations or mental deficiency or retardation. Routine laboratory investigations including complete blood count, liver and renal functions, ultrasound abdomen were normal. Audiometry of all four patients showed bilateral sensorineural deafness.

The physical examination of parents and rest of the siblings of all four patients did not reveal any abnormality of hair, eyes and skin color. However, two siblings had extensive freckling over face. The pedigree of the family is depicted in **Figure 9**.

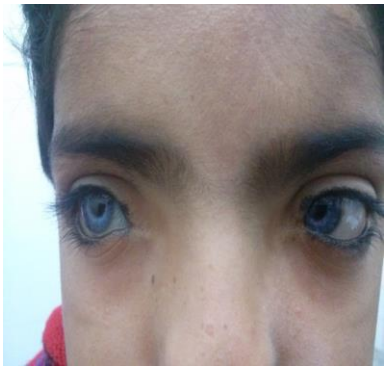

Figure 7 Blue eyes, broad nasal root, dystopia canthorum, synophrys, freckles

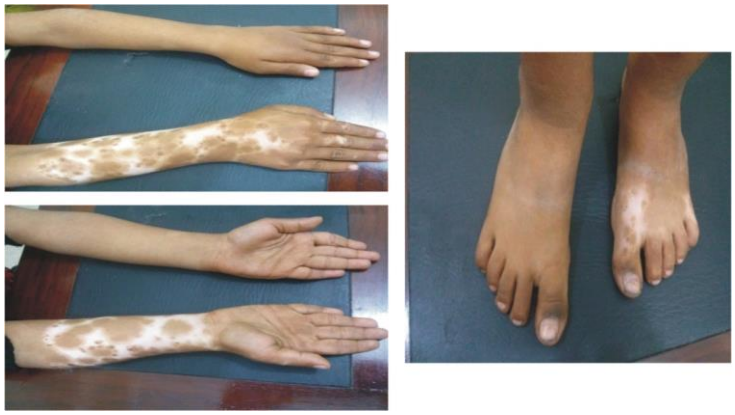

Figure 8 Hypopigmented patches over limbs

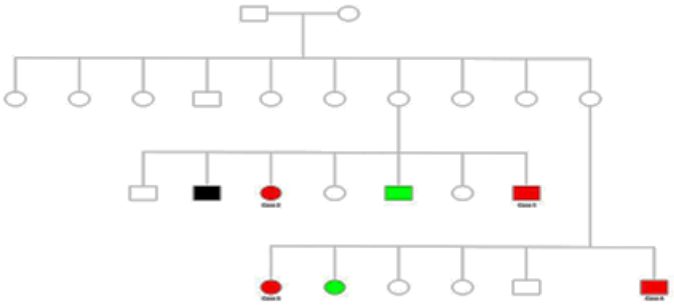

Figure 9 Red square: affected male, red circle: affected female, green: freckles, black: dead.

Table 1 Diagnostic criteria of Waardenburg syndrome [5].

	Major criteria	*Minor criteria*
1	Sensorineural hearing loss	Skin hypopigmentation
2	Heterochromic irides, Bicolor iris or brilliant blue iris	Synophrys
3	Hair hypopigmentation or white forelock or white hair at other body sites	Broad nasal root/ Dystopia canthorum
4	Dystopia canthorum	Hypoplasia of alae nasi
5	Presence of 1st degree relatives previously diagnosed	Premature graying of hair (before 30 years)

All these features favor the diagnosis of classical type I Waardenburg syndrome according to diagnostic criteria **(Table 1)**.

Discussion

The presence of freckles along with features of WS-I in all the affected persons of this family constitute a finding that has not been reported locally till date to the best of our knowledge. Previously only one study from China described freckles in association with WS.

Waardenburg syndrome is an autosomally inherited disorder with distinct morphological presentation.[3] There is no gender or racial predilection. There are 4 variants of WS according to clinical presentation, however genetic studies show more than 9 subtypes.

WS can be inherited as dominant or recessive trait having variable penetrance and expression leading to milder or incomplete phenotypes. Mutations of different genes like MITF, PAX3, SOX, END3-B have been reported in different subtypes of this syndrome.[4,5] Waardenburg consortium suggests diagnostic criteria **(Table 1)** so the diagnosis is essentially clinical. WS I (classical) and WS II are most common and share almost similar characteristics except that WS II lacks dystopia canthorum. Type III (Klein Waardenburg syndrome) has limb abnormalities while type IV is associated with Hirschsprung's disease (Shah Waardenburg syndrome).

Ziprkowski-Margolis or Woolf syndrome makes a close differential diagnosis. This is an X-linked recessive disorder that share many characteristics of WS like congenital deaf-mutism, heterochromic irides, piebald like skin patches and hair hypopigmentation.[3] Presence of typical facial features along with involvement of both male and female members in same generation favors autosomal inheritance thus making diagnosis of Waardenburg syndrome more likely in our series.

Vogt-Koyanagi-Harada syndrome (VKHS) features vitiligo, poliosis and eye abnormalities but there is no deafness. Absence of uveitis, signs and symptoms of miningismus, tinnitus, and alopecia excludes the VKHS.

Alezzandrini syndrome presents with unilateral facial vitiligo, unilateral retinal degeneration, grey hair and congenital deafness. But there are no morphological features related to eyes in this syndrome making diagnosis of WS more likely.

There is no definitive treatment for WS. Early diagnosis of these patients can lead to early rehabilitation and vocational training. This can prevent significant social dependence of patient and financial burden over family and society. Also gene mapping may lead to identification of different mutation or additional gene in this case as a rare clinical feature i.e. freckles, suggests or it could be an incidental finding.

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