Neurological Waardenburg-Shah syndrome: a diagnostic challenge in a child with skin hypopigmentation and neurological manifestation

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SUMMARY

Peripheral demyelinating neuropathy, central dysmyelinating leukodystrophy, Waardenburg syndrome and Hirschsprung disease (PCWH) is a rare manifestation of Waardenburg-Shah syndrome associated with mutations in the *SOX10* gene. The phenotypic expression is variable, thus presenting a diagnostic challenge. Clinical manifestations of PCWH may mimic other neurocutaneous syndromes. A thorough history, careful physical examination, appropriate imaging studies and an index of suspicion are needed to diagnose this condition. We describe an adolescent girl with skin hypopigmentation and blue irides associated with sensorineural hearing loss, Hirschsprung disease, as well as seizures with neurological signs, and discuss the challenges in diagnosing PCWH.

BACKGROUND

Waardenburg syndrome (WS) is a rare genetic disorder classically associated with congenital hearing loss, abnormal development of the intraocular region and pigmentation disorder of the skin, hair and eyes.[1] The condition is classified into Types I–IV based on the additionally associated features such as musculoskeletal involvement in Type III and Hirschsprung disease in Type IV.[1 2] WS Type IV, also known as Waardenburg-Shah syndrome (WS4), accounts for less than 100 cases reported until 2018 and an estimated prevalence of less than one per million population.[3]

The clinical presentation in WS4 is heterogeneous, but its major associations include abnormal pigmentation of the hair, skin or iris, sensorineural hearing loss and Hirschsprung disease. WS4 is linked to mutations in the *Endothelin-B receptor* (*EDNRB*), *Endothelin 3* (*EDN3*) and *SOX10* genes.[4] Even more rarely, WS4 may be associated with neurological manifestations such as intellectual disability, peripheral neuropathy and seizures. Mutations in the *SOX10* gene is also linked to this neurological variant of WS4, known as peripheral demyelinating neuropathy, central dysmyelinating leukodystrophy, WS and Hirschsprung disease (PCWH).[4 5]

The neurological presentation of mixed upper and lower motor neuron signs is consistent with abnormal central myelination seen on brain imaging and peripheral neuropathy seen on the nerve conduction studies.[5] Though the diagnosis of WS4 can be made clinically, the heterogeneous presentation combined with the mixed neurological signs can complicate and delay the diagnosis. In such circumstances, genetic testing may help to confirm the diagnosis and later guide accurate genetic counselling and individually tailored management.

We present a case of a girl with Hirschsprung disease associated with bilateral congenital sensorineural hearing loss, skin hypopigmentation, blue irides and neurological signs due to *SOX10* heterozygous mutation, leading to PCWH syndrome. We highlight the challenges and discuss the diagnostic considerations to help distinguish her clinical signs from other diseases with similar presentations.

CASE PRESENTATION

This is an early adolescent girl, born term to non-consanguineous healthy parents after an uneventful pregnancy and had a normal Apgar score. She has three other healthy older siblings. There is no family history of congenital or neurological diseases.

She developed multiple episodes of vomiting on the first day of life with delayed passage of meconium. Abdominal radiograph showed dilated bowels with absent distal bowel gas. Hirschsprung disease was suspected and confirmed by a rectal biopsy, which showed the absence of ganglion cells in the submucosal plexus. Daily rectal washout was given. She had a transanal pull-through surgery 3 months later, which showed the transitional zone at the upper rectum.

During her late neonatal period, focal areas of skin hypopigmentation were noted over bilateral lower limbs, dorsum of bilateral hands sparing the palms (figure 1A) and over the anterior neck. The hypopigmented patches were punctuated with islands of pigmented macules (figure 1B). The distribution pattern is non-specific and does not follow the Blaschko lines. She has no white forelocks. The dermatologist diagnosed vitiligo and started her on emollients and topical steroids.

At early infancy, cerebellar signs as evidenced by bilateral horizontal nystagmus with involuntary tremors of all limbs and the head were noted during review. An urgent CT scan of the brain showed no structural abnormalities. Ophthalmology assessment revealed bilateral blue irides (figure 1C), and funduscopy showed choroidal hypopigmentation. Given the skin hypopigmentation and the ocular findings, a diagnosis of partial albinism was made.

The cerebellar signs progressively worsened with age, associated with significant global developmental

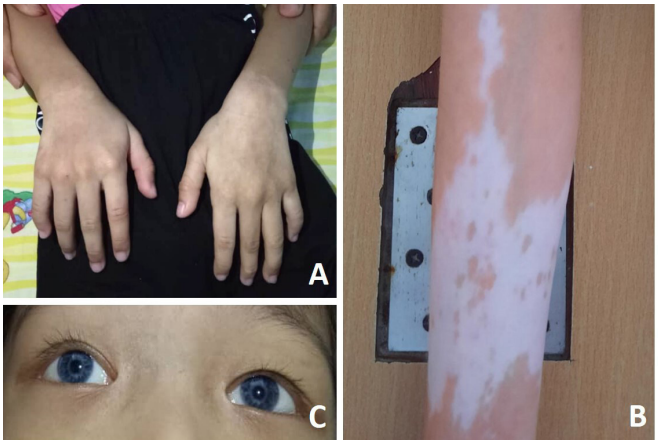

Figure 1 (A) Bilateral dorsum of the hands with less prominent hypopigmentation extending to the distal forearms but sparing the palms. (B) Hypopigmented patch over the right calf with sharply defined, irregular borders and pigmented islands scattered throughout the achromic patch. The lesions are not confined to any specific patterns or lines of Blaschko. (C) Bilateral blue irides with horizontal nystagmus but no evidence of telecanthus (dystopia canthorum), synophrys or broad nasal root. (Latest pictures taken in 2022.)

delay. She had poor truncal tone causing difficulty to sit unsupported and ambulate. Her speech was also markedly impaired with no spoken words. An auditory brainstem response done as a toddler to investigate the speech delay showed bilateral profound sensorineural hearing loss. No provisional diagnosis was given until a few years later, when Hypomelanosis of Ito was suspected, given her neurological signs and cutaneous findings.

The first episode of seizure occurred in her late childhood, which was generalised with tonic and clonic movement of all limbs. The seizure lasted for 3 min and self-aborted with a brief postictal drowsiness. She had no clinical features of meningitis and was afebrile during the presentation.

On examination, she was severely underweight with a weight of 18.5 kg (<3rd percentile), height 135 cm (<3rd percentile) and body mass index (BMI) 10.2 kg/m^2 (<3rd percentile). Neurological examination showed ataxia and hypotonic posture with severe atrophy of all four limbs (figure 2). Her upper limbs demonstrated a Medical Research Council muscle strength grading of 3, while her lower limbs were graded 2. Deep tendon reflexes were absent, with contracture of bilateral ankles. Babinski reflexes were down-going, and no ankle clonus was elicited. There was a lack of withdrawal response to pain

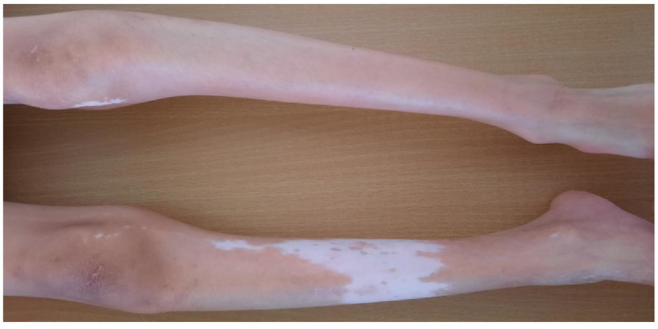

Figure 2 Bilateral lower limbs with asymmetrical hypopigmented patches and severe wasting of the muscles. (Latest picture taken in 2022.)

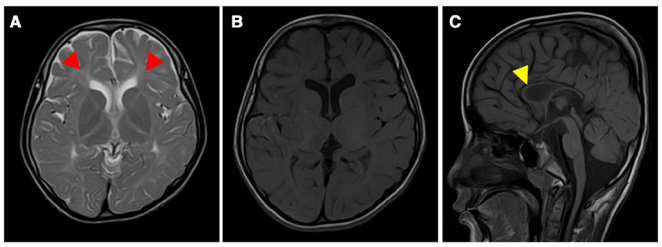

Figure 3 (A) Axial MRI T2-weighted image shows diffuse, symmetrical hyperintensity of bilateral cerebral white matter (red arrows). (B) Axial T1-weighted sequence shows a symmetrical isointense signal of the white matter in keeping with generalised dysmyelination of the white matter. (C) Sagittal T1-weighted image shows a thin and dysplastic corpus callosum (yellow arrow).

stimulus, suggesting reduced sensation, particularly over the lower limbs. Limited cranial nerves assessment revealed bilateral horizontal nystagmus with intact vision. Abdomen was scaphoid with no palpable mass or hepatosplenomegaly. Her respiratory and cardiovascular examination were unremarkable.

INVESTIGATIONS

MRI of the brain was done after the new onset of seizure. There was hesitancy to consent for MRI earlier as the parents had come to terms with the child's disabilities and were doubtful of the value of the MRI in changing the disease outcome. Her scan showed generalised dysmyelination of the white matter with thin and dysplastic corpus callosum (figure 3A–C). An electroencephalogram done at the same time was reported as normal. Nerve conduction study was not available in our centre.

The combination of skin hypopigmentation, bilateral blue irides, sensorineural hearing loss and Hirschsprung disease was consistent with WS4, but neurological signs are uncommonly described. The family was counselled for genetic study to help solve this diagnostic dilemma. The genetic test is expensive and not readily available in our centre, and it was not pursued until research funding became available 2 years later. The whole exome sequencing detected a heterozygous mutation in the *SOX10* gene *NM_006941.1:c.1400_*10del(NP_008872.1:p.*467Cysext*82)*. This mutation is consistent with PCWH syndrome, a more severe phenotype of WS4.

DIFFERENTIAL DIAGNOSIS

While congenital skin hypopigmentation, sensorineural hearing loss and iris homochromia were suggestive of WS, the presence of neurological signs is much less described in WS. Therefore, other differential diagnoses, particularly neurocutaneous syndromes, should be considered (table 1).

TREATMENT

Sodium valproate was started, and the seizures improved with treatment. Her seizure is well controlled now with a sodium valproate dose of 10 mg/kg two times per day. Physiotherapy and occupational therapy were started from early infancy when the motor delay was detected. Hearing aid had been employed with regular review by the audiologists after detecting hearing loss.

OUTCOME AND FOLLOW-UP

Currently, she requires assistance with all her daily activities. She relies on her parents for mobility using a wheel-chair. Due to her poor truncal tone, she needs support to help her sit erect. She

Table 1 Differential diagnosis of peripheral demyelinating neuropathy, central dysmyelinating leukodystrophy, Waardenburg syndrome and Hirschsprung disease

Disease/condition	Supporting features	Differentiating features
Hypomcelanosis of Ito	► Congenital hypopigmentation of the skin ► Subtle iris and choroidal hypopigmentation[10] ► Seizure and intellectual disability ► Ataxia, neuropathy, hypotonia and hearing loss ► MRI may show white matter abnormalities (involving the parietal periventricular and deep cortical white matter) and hypoplastic corpus callosum[11]	► Pattern of hypopigmentation usually unilateral, Blaschkoid patches, whorls or streaks ► Ocular findings are seen in a quarter of patients but are generally non-specific such as corneal asymmetry, cataracts and micro or macrophthalmos[10] ► Not associated with Hirschsprung disease ► May have hemihypertrophy on the side of hypopigmentation ► Other brain imaging findings include neuronal heterotropias, hemimegalencephaly and cerebellar hypoplasia[11]
Tuberous sclerosis (TS)	► Skin hypopigmentation (ash-leaf macules) ► Seizures and developmental delay	► Brain imaging typically shows subependymal hamartomas and subcortical tubers ► White matter changes on MRI usually demonstrate more distinct patterns such as thin bands of abnormal signal intensities or wedge-shaped lesions[11] ► No other major cutaneous features of TS such as shagreen patch and angiofibroma ► Most common eye finding is ocular hamartoma and, very rarely, hypopigmented iris spots[12]
Vitiligo (segmental)	► Patches of skin hypopigmentation and asymmetrical distribution	► Not usually associated with any neurological/extracutaneous manifestations ► No iris involvement ► Usually acquired
Partial albinism	► Patches of skin hypopigmentation and white forelock	► Extracutaneous and ocular manifestations are not described[12]

has limited comprehension of verbal instructions and attends a special education class with support from the teachers. She is severely underweight, but as she can still swallow safely, her parents had opted not for tube feeding presently. However, the dieticians are working closely to optimise her nutrition. If the need arises, tube feeding should be reconsidered.

DISCUSSION

WS4 is a rare genetic disease characterised by abnormal pigmentation of the hair, skin or iris, sensorineural hearing loss and Hirschsprung disease. WS4 is associated with gene mutations in the *EDNRB*, which is responsible for an endothelin receptor; *EDN3*, which encodes for the ligands of the endothelin receptor; and the *SOX10* gene, encoding the transcription factor SOX10.[4] Truncating mutation in *SOX10* is linked to a more severe phenotype known as PCWH.

The *SOX10* gene is located on chromosome 22q13 and is an important regulator of neural crest development.[4 5] Neural crest cells are multipotent cells originating from the neuroepithelium of the neural tube, which migrates to the different parts of the embryo to form the melanocytes, enteric ganglia as well as control the proliferation and differentiation of Schwann cells in the peripheral nerves and oligodendrocytes in the central nervous system (CNS).[6 7] Inactivation of the *SOX10* gene due to the mutation results in the loss of the neurons and glial cells in the nervous system, enteric ganglia and skin hypopigmentation.[6] Our child has a heterozygous mutation in the *SOX10* gene *NM_006941.1:c.1400_*10del(NP_008872.1:p.*467Cysext*82)*. This leads to a pathogenic loss-of-stop variant that changes the length of the protein and disrupts its function giving the phenotypes observed in PCWH.

PCWH presents with a mixed motor neuron sign which are rarely described in WS4. Peripheral neuropathy is characterised by severe muscle wasting and hyporeflexia which can be objectively demonstrated by abnormal velocity on nerve conduction study and reduced myelination on histopathological study of nerve biopsies.[7] CNS involvement is characterised by clinical signs such as hypotonia, ataxia, spasticity, seizures and intellectual disability. An MRI can confirm CNS involvement, typically showing evidence of dysmyelination.[7]

MRI changes may be detected earlier during infancy and early childhood to show hypomyelination, but these may later be replaced by newly formed dysfunctional myelin as described by Verheij *et al*.[4] The presence of complex neurological signs coupled with skin pigmentation defects can often mislead clinicians to suspect other neurocutaneous syndromes. White matter changes are commonly reported in neurocutaneous syndromes. Nevertheless, the presence of dysmyelination of the white matter on MRI combined with lower motor neuron signs and Hirschsprung disease should raise the suspicion of PCWH.

In our case, the MRI was done much later showing generalised dysmyelination. Similarly, genetic testing was only done 2 years later after the initial suspicion of the disease. Ideally, these investigations should have been done earlier, but the parents in our case had already come to terms with the child's condition, hence deciding not to investigate further. Moreover, there is a possibility that the costly genetic test may not be able to provide the desired answers. In such a scenario, where the benefits of reaching a diagnosis are uncertain and a delay in costly investigation poses no immediate harm to the child, the 'zone of parental discretion' to not pursue further investigations should be respected.[8] However, as demonstrated in our case, we need to recognise that parents' decisions are dynamic and should be revisited, especially when these tests become life-saving or readily available. Genetic confirmation may not alter the management, but the value of the test in these situations is to provide a better understanding of the disease and the possibility of identifying the aetiology.[9] For our child, the genetic results improved the parents' understanding and expectations of the disease, besides giving closure.

A holistic, multidisciplinary care is imperative for this complex, rare disorder. Hearing aid may improve some degree of hearing for some. Nutritional rehabilitation is particularly important as these individuals are mostly undernourished. Sometimes Ryle's tube feeding or gastrostomy has to be considered. This option should be discussed openly with the caretakers. Lastly, a good educational support for the child, together with psychosocial support for the caretakers, is essential.

In conclusion, PCWH can often be misdiagnosed due to the heterogeneity of the clinical presentation. Despite possessing the same genetic mutation, the phenotype expression may differ among patients, making the diagnosis extremely challenging.

Patient's perspective

Narrated by the child's mother:

When our little girl was born, she was perfect and well. We have three other children, who are fit and well. The doctor told us that my pregnancy was normal and when she was born, they also reassured that she was healthy. However, she started vomiting a day after and her tummy became distended. The doctors told us that there was a problem with her gut, and she would need help to evacuate her stool, and later, a surgery. It was hard to swallow, but we soldiered on, doing the bowel cleaning religiously. To a non-medical person, it was a daunting experience.

We were slapped with more bad news during her early infancy. She started having abnormal eye movement and her limbs too. I recalled vividly how we were asked multiple times about her abnormal movement and if it had just occurred. Did I notice that her eyes were blue from birth? It was confusing to me. From here on, it was just a downward spiral. Her movement problems got worse with time. She had a lot of tremors and she needed a lot of assistance with her daily activities. She could not speak, and she could not hear. Seeing her watch her siblings play but not being able to join them, is heart-breaking.

We remained optimistic about our child's condition. The eye doctors said she has unique blue eyes but not related to her illness. Seeing the skin doctors, they reassured us it was just skin loss of colour. A few years later, the children's doctor concluded that her disorder might be consistent with Hypomelanosis of Ito. With that, her prognosis and recovery would be poor. We came to terms with the diagnosis. I knew as a mother, I could only provide and care for her as much as I could to support her. We sent her regularly for physiotherapy, and to special education classes. We did not consider further imaging and work-up as we felt she has had enough investigation done on her, and there is no chance of a 'cure'. We just wanted to make sure she was cared for and happy.

Fast forward a few years later, the doctors reassessed her case and thought her condition might be more consistent with Waardenburg-Shah syndrome. Then came the discussion of sending a genetic work-up for her to confirm this. So, for once, in many years, we were offered a different diagnosis, but ultimately, to our dismay, confirming this diagnosis would not change the outcome for our girl. We did seriously give the notion a thought, but the price for the test was so exorbitant and with our meagre income, it was impossible. I felt sorry for not being able to offer more for my child, but we did try by other means. So, we put this idea to rest.

She had her first fit in her late childhood. After much thought, we agreed to do the MRI scan. It showed abnormalities in the protective layers of brain's nerves, which could explain the fits. Fortunately, with medication, she did not have many recurrences. Two years later, we were told we could send off the genetic test as part of research collaboration at no cost. We did not hesitate this time, because, to be honest, as far deep as we had buried our hopes, we still wanted to know if there was an alternative answer to her condition. Is there anything at all that could change the course of the disease? We met with the doctors when the results were available. Then we were told it was the more severe form of the suspected disease. Were we disappointed? Not as much as we thought. We have a clear answer for our child's diagnosis. At least now, we can put to rest

Continued

Patient's perspective Continued

the years of asking, 'What is wrong with my daughter? Did we miss anything?'

Though there is no treatment for her condition, we are grateful we have an answer. Now we know we can concentrate on meeting her needs and making her happy, in our little ways. I often looked back and pondered, if we had taken the chances to do those scans and work-up earlier, would it have changed the outcome for her? There has always been a lot of self-blame. Though deep down we knew there was no cure, this confirmation of her condition has at least helped us to understand better what her disease is and to support her better now.

Learning points

- Waardenburg-Shah syndrome (WS4) should be considered in the presence of skin hypopigmentation, blue irides, sensorineural hearing loss and Hirschsprung disease.
- Peripheral demyelinating neuropathy, central dysmyelinating leukodystrophy, Waardenburg syndrome and Hirschsprung disease (PCWH) is a more severe form of WS4 associated with neurological signs linked to *SOX10* gene mutation. Genetic confirmation should be pursued to assist in counselling and to optimise management.
- The heterogeneity of the presentations in PCWH makes it challenging to diagnose and can often be misdiagnosed for other neurocutaneous syndromes.
- Brain MRI should be done early to look for features of dysmyelination, suggestive of PCWH.
- The involvement of a multidisciplinary team is crucial for the optimal care of this complex disorder.

The awareness of the disease, coupled with a detailed history taking, physical examination, imaging studies and a high index of suspicion, is crucial to diagnose the disease. Managing a child with rare disease is an arduous task; while early diagnosis is important, this should be balanced against the cost and emotional implications of this pursuit to the family.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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