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Zuelzer Wilson syndrome with Waardenberg syndrome: A morbid combination of Neurocristopathies

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ABSTRACT

Neurocristopathy refer to a diverse group of congenital disorders that arise due to defects in the migration, growth or specialization of neural crest cells during early embryonic development. These cells contribute to the development of melanocytes, enteric ganglia, and autonomic nervous system structures. We report a rare and complex case of neonate with combination of Waardenburg syndrome with Zuelzer-Wilson syndrome both united by a defective neural crest development (1,2).

The neonate was brought on the fifth day of life with progressive abdominal distention, bilious vomiting, and an absence of meconium passage since birth. Clinical features were indicative of a lower gastrointestinal obstruction. The notable features included a white forelock, anisocoria, and multiple de-pigmented macules all pointing towards a diagnosis of Waardenburg's syndrome. The patient Underwent contrast study suggestive of Hirschsprung's disease. Surgical exploration and histopathological livering biopsies revealed total colonic agenesis with consistent with Hirshsprung's disease of syndromic origin with Zuelzer-Wilson syndrome.

The consistence of these two disorders in a single patient is rare and represents a massive failure of neural crest migration. This case highlights the importance of detailed physical examination and early surgical and genetic evaluation in neonates with multisystemic manifestations of neural crest dysfunction early.

1. INTRODUCTION

Neural crest cells are pluripotent embryonic cells that migrate extensively to contribute to the development of multiple organ systems, including the craniofacial skeleton, melanocytes, peripheral enteric nervous system, retina, adrenal gland and components of the cardiac outflow tract. Defects in the migration, survival, or differentiation of these cells can lead to a group of disorders collectively known as neurocristopathies (3). Among these, Waardenburg syndrome and Zuelzer-Wilson syndrome represents well-characterized but rarely overlapping phenotypes (4).

Waardenburg syndrome is a genetically and phenotypically heterogeneous disorder, primarily affecting melanocyte development representing in depigmentation of the skin, hair, and irises. It is classified into four types based on clinical features and genetic mutations (5). Genotype 4, also known as Shah-Waardenburg syndrome, is characterized by depigmentation, abnormalities, and congenital aganglionic megacolon resulting from mutations in genes such as SOX10, EDNRB, and EDN3, all critical to neural crest functions (6,7)

The combination of Zuelzer-Wilson syndrome and Waardenburg syndrome can be morbid and also can be mortal in some cases (8). The early identification clinically and confirmation by genetic studies leads to proper counseling of parents and helps to set achievable targets with respect to the surgeries and the long-term outcomes (9).

Hence, recognition of these two pathologies can lead to timely surgical intervention, targeted multidisciplinary support, and genetic counseling to optimize both immediate care and long-term outcomes.

Case presentation:

A 5-day-old male infant delivered to non-consanguineous parents was admitted to the neonatal intensive care unit with outgoing abdomen distention, bilious vomiting, and an absence of meconium passage since birth.

Birth and perinatal history:

The baby was delivered via full-term normal vaginal delivery at 36 weeks of gestation to a gravida 3 para 2 mother with no reported antenatal diagnosis of diseases. Birth weight was 2.2 kg and APGAR score was reportedly normal. However, by the second day of life, the neonate developed cyanosis, poor feeding, hypoglycemia, and lethargy, necessitating NICU admission.

The baby was noted to be hypotonic with a poor cry and experienced episodes of shallow breathing, particularly during sleep, which were not initially recognized as significant. There was no family history of similar complaints, pigmentary disorders, or genetic syndromes.

Phenotypic examination findings:

At presentation, the baby's general condition was fair with a heart rate of 132 bpm, respiratory rate of 42 per minute, and oxygen saturation of 98% on room air. On detailed physical examination, several striking phenotypic anomalies were noted.

piebaldism, another pigmentary disorder involving congenital leukoderma and white forelock also results from defective melanocyte migration. Though clinically distinct from Waardenburg syndrome, phenotypic overlap occurs, particularly in patients with SOX10-related mutations.

In this case, we describe a neonate presenting with total colonic agangliogenesis, classical pigmentary anomalies, and indicating a syndromic overlap of Waardenburg syndrome and Zuelzer- Wilson syndrome and piebaldism. The convergence of these entities in a single patient underscores a profound failure of neural crest development and highlights the need for a multidisciplinary approach encompassing neonatology, pediatric surgery, genetic, pathology and endocrinology.

Through this report we aim to shed light on the importance of recognizing neonatal phenotypic clues, the role of early histopathological confirmation and the significance of considering rare neurochristopathy overlaps in patient with multidisciplinary presentations at birth.

Hair and skin:

A prominent white forelock (piebaldism) over the frontal scalp, multiple hypopigmented macules over the trunk and limbs, and café au lait-like macules over the chest and hands.

Eyes:

Bilateral bright blue irises, iridial hypopigmentation with no apparent strabismus or visual tracking difficulty with slight anisochoria present.

Craniofacial features:

Normal facial symmetry, no dystopia canthorum, low anterior hairline or other major dysmorphisms.

Abdomen:

Gaseous distension present, soft and non-tender, bowel sounds were sluggish. On perectal examination, explosive passage of flatus is present.

The combination of intestinal obstruction, white forelock, hypopigmentation of skin, and blue irides promoted clinical suspicion of Waardenburg syndrome, specifically a type 4, which is known to be associated with Hirschsprung's disease. Here unlike the short and long segment Hirschsprung disease, it was complete colonic aganglionosis suspicious of Zulzer-Wilson syndrome.

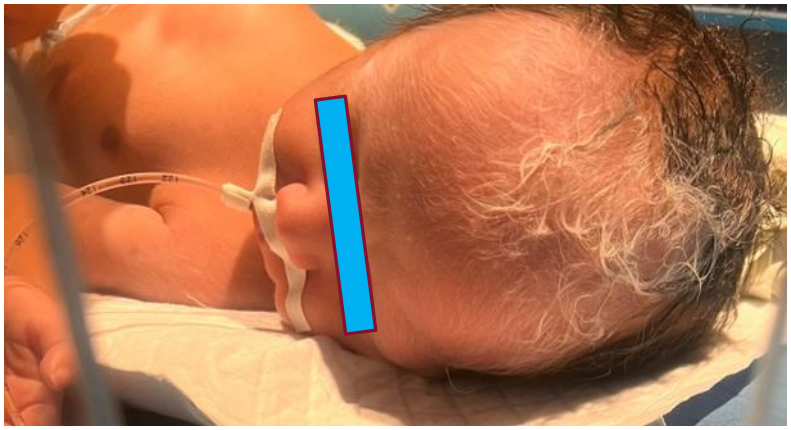

Figure 1 Close-up view of a neonate with a sharply demarcated white forelock—an iconic pigmentary manifestation of Waardenburg syndrome—alongside nasal oxygen support and nasogastric tube placement.

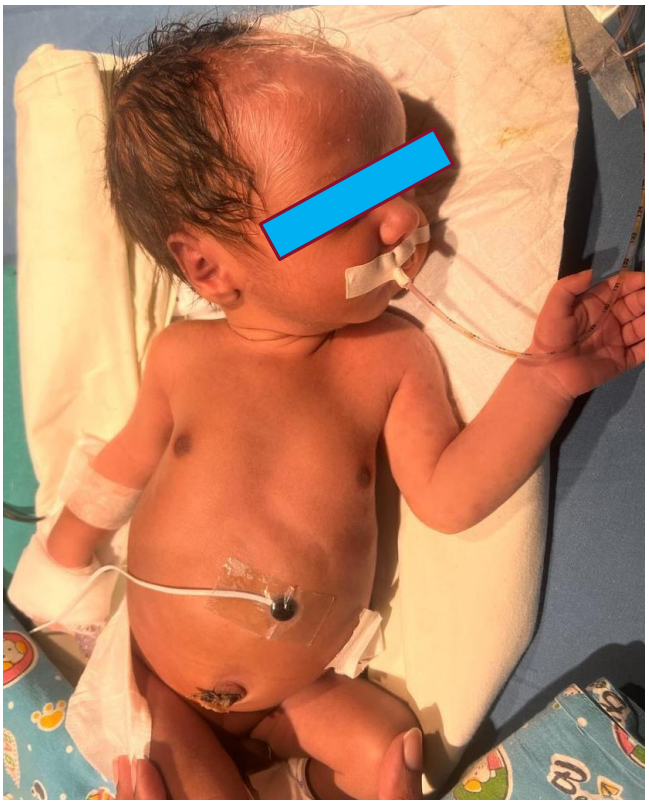

Figure 2: Full-body image of a neonate with frontal white forelock, nasogastric tube, peripheral IV access, and visible umbilical stoma, suggesting a diagnosis of Waardenburg syndrome with possible total colonic aganglionosis (Hirschsprung disease variant).

Surgical intervention and biopsy:

Given the radiological and clinical evidence of bowel obstruction, the neonate had undergone exploratory laparotomy and ileostomy at the index hospital. During surgery, the entire colon appeared narrow and collapsed with a transition zone noted in the distal ileum. Multiple leveling biopsies were taken from the colon, sigmoid, ileum, appendix and the ileostomy site to assess the presence of ganglion cells.

Picture:

Collapsed large bowel and dilated small bowel.

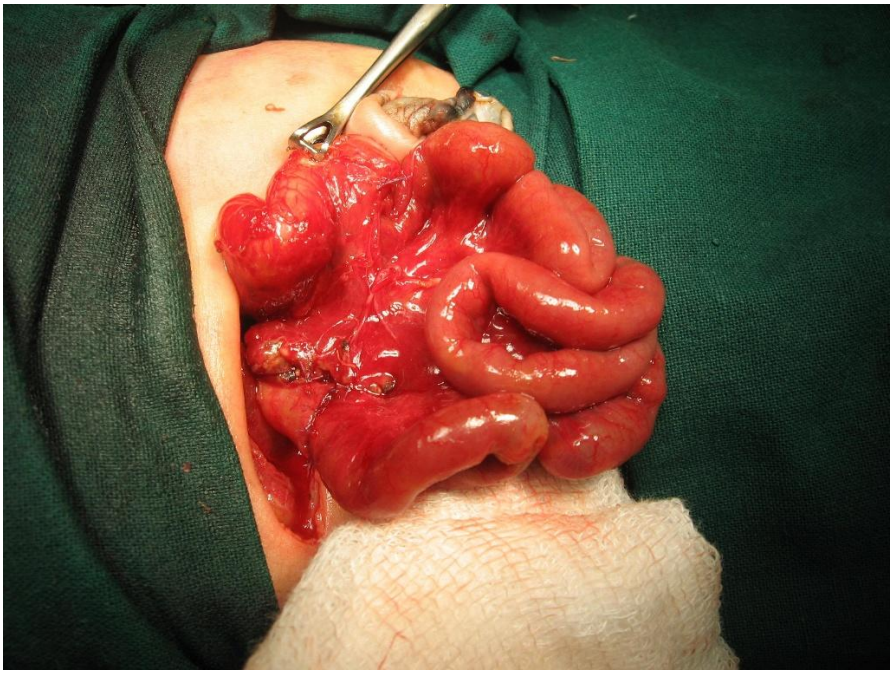

Figure 3: Intraoperative image of a neonate showing distended, healthy-appearing small intestinal loops with collapsed colon, suggestive of total colonic aganglionosis (TCA). The procedure was performed via right supra umbilical transverse incision, laparotomy and biopsies (seromuscular) confirmed aganglionosis extending from the rectum through the colon.

Initial investigations

Laboratory evaluation revealed the following

Table 1:

Hemoglobin	11.4 g/dl
Total WBC count	10,600 /mm3
Platelet count	256,000 /mm3
Serum sodium	132 mmol/L
Serum potassium	4.2 mmol/L
Serum calcium	7.9 mg/dl
CRP	2.2 mg/dl
Urine reducing substances	Negative

Imaging studies:

Revealed dilated intestinal loops accompanied by air-fluid levels pointing towards a likely obstruction in the distal bowel. Imaging studies were suggestive of Zulzer-Wilson syndrome, total colonic aganglionosis.

Cranial ultrasound:

Demonstrated a persistent cavum septum pellucidum, which may be seen in some neurodevelopmental disorders, but was otherwise unremarkable.

The pathology report (SD952-2025) from a senior surgical pathologist confirmed absence of aganglion cells in specimens from the colon, sigmoid colon, and terminal ileum, while ganglion cells were present in the ileostomy site, indicating the level of transition and confirming the diagnosis of total colonic aganglionosis. These findings were consistent with Zulzer-Wilson syndrome.

Postoperative course:

The infant was managed with IV fluid, broad-spectrum antibiotics, analgesics, and supportive care. He was gradually

started on feeds through the ileostomy, which functioned adequately. Genetic testing for PHOX2B mutation typically associated with CCHS was planned, in following period.

Figure 4: Clinical image of a syndromic infant presenting with white forelock, depigmented skin patches, and postoperative stoma care.

2. DISCUSSION

This case reflects a rare neurocristopathy combination.

Waardenberg syndrome (10,11):

Defined by pigmentary anomalies (white forelock, heterochromia, hypopigmented macules) and Hirschsprung's disease (11).

The presence of total colonic aganglionosis, though less common, has been documented in several subtypes (12)

Caused by mutations in genes like EDNRB, EDN3, and SOX10, which was vital for neural crest migration.

Zuelzer-Wilson syndrome:

Complete colonic aganglionosis

microlon

PHOX2B gene mutation.

Piebaldism:

A congenital disorder of melanocyte migration marked by white forelock and hypopigmented patches, consistent with this child's appearance.

Frequently overlaps with Waardenberg phenotype due to shared developmental origin from neural crest.

The combination of total colonic aganglionosis, piebaldism, and waardenberg syndrome in a single neonate is a diagnostic clue to waardenberg with Zuelzer- Wilson syndrome, making genetic testing and long-term monitoring essential (13).

Early identification is critical to:

Plan definitive surgical treatment for Hirschsprung's disease. Identification of complications of Waardenberg syndrome. Provide genetic counseling to the family.

3. CONCLUSION

This case emphasized the necessity of integrating phenotypic observations, histopathological confirmation and clinical suspicion of autonomic dysfunction in neonates with intestinal obstruction and pigmentary anomalies. The diagnosis of Waardenberg syndrome with total colonic aganglionosis underscores the complex spectrum of neurocristopathy and the values of multidisciplinary early interventions to reduce morbidity and mortality.

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