Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14, Issue 32s (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

A Rare Neurocristopathy Overlap: Coexistence of Haddad and Waardenburg Syndromes in a Neonate

Dr. Anusha Shridhar [1], Dr. Santosh B Kurbet [2], Dr. Roopa M Bellad [3], Dr. Vineeta Gautam [4], Dr. Smruthi Rugi[5]

[1]Junior resident- II MBBS, M.D paediatrics, Department of paediatrics, JNMC, Belgavi

Email ID: anushashridhar97@gmail.com

[2]Professor and HOD, M.S., M.Ch (paediatric surgery), DNB, Department of paediatric surgery, JNMC, Belagavi

Email ID : drsantoshbkurbet4@gmail.com

[3]Professor D.C.H., M.DPaediatrics, Department of paediatrics, JNMC, Belagavi

Email ID : belladroopa5@gmail.com

[4]Senior resident, D.C.H., D.N.BPaediatrics, Department of paediatrics, JNMC,Belagavi

Email ID: vineeta.bims@gmail.com

[5]Senior resident, MBBS, M.D Paediatrics, Department of paediatrics, JNMC,Belagavi

Email ID : smruthirugi94@gmail.com

Cite this paper as: Dr. Anusha Shridhar, Dr. Santosh B Kurbet , Dr. Roopa M Bellad , Dr. Vineeta Gautam , Dr. Smruthi Rugi, (20y) A Case Report A Rare Neurocristopathy Overlap: Coexistence of Haddad and Waardenburg Syndromes in a Neonate. *Journal of Neonatal Surgery*, 14 (32s), 3234-3241.

ABSTRACT

Haddad syndrome, defined by the dual presence of congenital central hypoventilation syndrome (CCHS) and Hirschsprung disease (HD), represents a rare neurocristopathy with significant morbidity. Waardenburg syndrome (WS), characterized by pigmentary anomalies, sensorineural deafness, and mutations affecting neural crest derivatives, has not previously been described in combination with Haddad syndrome. We report a unique case of a term male neonate who presented with abdominal distension, aganglionic megacolon, and progressive hypoventilation within 48 hours of life. Distinctive phenotypic features—including a white forelock, hypopigmented skin patches, and vivid blue irides—raised early suspicion of WS. Levelling biopsies confirmed total colonic aganglionosis, while a PHOX2B poly alanine expansion mutation established the diagnosis of CCHS. This dual diagnosis constitutes a previously unreported neurocristopathy overlap. Early phenotype driven recognition, timely surgical decompression, ventilatory support, conservative physiotherapy and long term multidisciplinary care were pivotal to outcome.

1. INTRODUCTION:

Neurocristopathies encompass a spectrum of congenital anomalies arising from defects in neural crest cell migration and differentiation. Haddad syndrome is a rare manifestation of this group, characterized by the simultaneous occurrence of congenital central hypoventilation syndrome (CCHS) and Hirschsprung disease (HD). (1) Waardenburg syndrome (WS), another neurocristopathy, involves pigmentary disturbances, sensorineural hearing loss, and various neural crest-derived tissue anomalies. Co-occurrence of Haddad and Waardenburg syndromes is exceedingly rare and previously undocumented in Indian literature.(2)

Haddad syndrome is most commonly attributed to mutations in the PHOX2B gene, leading to impaired autonomic regulation of respiration, particularly during sleep. Patients often require lifelong ventilatory support. (3) Concurrent HD presents as delayed meconium passage, abdominal distension, and intestinal obstruction due to absence of ganglion cells in the enteric nervous system. WS, particularly type IV (Shah-Waardenburg), shares genetic mutations such as EDNRB, EDN3, or SOX10, causing pigmentary anomalies and aganglionosis. (4)

We present a rare neonatal case exhibiting overlapping clinical features of both syndromes. This case underscores the complex genetic and embryological interactions of neural crest disorders and the need for high clinical suspicion in atypical neonatal presentations

2. CASE PRESENTATION

A male neonate was born at 38+1 weeks via normal vaginal delivery to a 27-year-old second gravida mother with second-degree consanguinity. The birth weight was 2.8 kg, with Apgar scores of 7 and 9 at 1 and 10 minutes, respectively. Antenatal scans revealed mild ventriculomegaly.

Within 36 hours of life, the neonate developed progressive abdominal distension, bilious vomiting, and failed to pass meconium. Phenotypic examination revealed hallmark features: a depigmented white forelock, hypopigmented skin patches, café-au-lait macules, and vivid blue irides. Initial stabilization involved nasogastric decompression, correction of hypoglycemia (lowest recorded glucose 36 mg/dL), broad-spectrum antibiotics (ciprofloxacin and amikacin), and fluid-electrolyte balance.

By day 2, the infant exhibited episodes of apnea and shallow breathing during sleep with hypercapnia, prompting suspicion of a central respiratory defect. Blood gas analysis showed elevated pCO2 levels.

Radiography showed grossly dilated bowel loops with absent rectal gas. Levelling biopsies confirmed total colonic aganglionosis extending to the distal ileum. An emergency laparotomy with loop ileostomy separated by skin bridge was performed on day 8. Intraoperative findings confirmed extensive aganglionosis.

Genetic testing confirmed a PHOX2B gene mutation, establishing the diagnosis of CCHS. Thus, the patient fulfilled diagnostic criteria for Haddad syndrome, in addition to fulfilling phenotypic and familial markers for WS type IV.

Typical Clinical Features of Haddad and Waardenburg Syndromes

Neonates with Haddad syndrome often present with life-threatening central hypoventilation, particularly during sleep, leading to hypercapnia, apneic episodes, and a need for mechanical ventilation. They also exhibit features of Hirschsprung disease such as delayed passage of meconium, abdominal distension, bilious vomiting, and intestinal obstruction, often requiring surgical intervention. On the other hand, Waardenburg syndrome is characterized by distinctive pigmentary anomalies (like a white forelock, hypopigmented skin patches, and vivid blue or heterochromatic irides), sensorineural hearing loss, and occasionally facial dysmorphism (broad nasal root, synophrys). In Type IV (Shah-Waardenburg), aganglionosis is a defining feature. The co-occurrence of these syndromes demands a high index of suspicion and careful evaluation of cutaneous, gastrointestinal, and respiratory symptoms in the neonatal period.

Initial Clinical Course (0–48 h)

The neonate presented with progressive abdominal distension was accompanied by bilious vomiting and an absence of meconium passage. On examination, distinctive phenotypic markers were noted, including a depigmented frontal forelock, several café-au-lait macules, hypopigmented cutaneous patches, and striking blue irides. Overnight observation revealed episodes of shallow breathing with resultant hypercapnia during sleep, raising concern for intermittent hypoventilation.

Stabilisation included nasogastric decompression, intravenous dextrose (hypoglycaemia 36 mg/dL), broad spectrum antibiotics (ciprofloxacin 20 mg/kg/day, amikacin 15 mg/kg/day), and fluid electrolyte correction.

Textbook Classification of Neurocristopathies

(Adapted from Bolande & Fernandez 1974; Kallianiotis 2023) (5)

Simple Neurocristopathies	**Complex Neurocristopathies**
Non-Neoplastic Dysgenetic	**Neoplastic and Non-Neoplastic**
- Hirschsprung's disease	- Neurofibromatosis (Von Recklinghausen disease)
- Albinism	- Multiple endocrine neoplasia (MEN) type 1
- Mandibulofacial dysostosis	- MEN2A
- Otocephaly	- MEN2B
- Congenital Central Hypoventilation	- Neurocutaneous melanosis
- Syndrome	- Familial neuroblastoma with Hirschsprung’s disease
	- CCHS + HSCR = Haddad syndrome
	- Waardenburg + HSCR = Shah Waardenburg Syndrome
Neoplastic	

Simple Neurocristopathies	Complex Neurocristopathies
- Neuroblastoma	
- Pheochromocytoma	
- Medullary thyroid carcinoma (MTC only)	
- Nonchromaffin paraganglioma	
- Carcinoid tumors	

Our patient fits the "Complex/Mixed" category, demonstrating pigmentary anomalies (WS), total colonic aganglionosis (HD), and autonomic hypoventilation (CCHS).

Radiography on day 2 displayed massively dilated bowel loops with absent rectal gas. Levelling biopsies confirmed total colonic aganglionosis extending to the distal ileum. An emergency laparotomy with loop ileostomy was performed on day 8. PHOX2B gene testing later revealed a 27 polyalanine expansion mutation (20/27 genotype), consistent with CCHS.

3. TIMELINE OF EVENTS

Day	Clinical Event
Birth	Term NVD (38 + 1 weeks), 2.8 kg; Apgar 7/10, 9/10
0–1	Abdominal distension; no meconium; hypoglycaemia correction
2	Hypercapnic episodes; radiograph & biopsy initiated
3–5	Biopsy confirmed total colonic aganglionosis
8	Emergency laparotomy + loop ileostomy
10	Phototherapy; direct breastfeeding resumed
12	PHOX2B mutation analysis sent
14	PHOX2B expansion confirmed → Haddad diagnosis finalised
15	Discharged; home apnea monitor + stoma care education

4. INVESTIGATIONS

• 18 Oct 2024: Hemoglobin 15 g/dL, direct Coombs test negative, peripheral smear normocytic normochromic; blood culture no growth.

• 20 Oct 2024: Hb 16.1 g/dL, WBC 14,500/µL, platelets 306 × 10^3/µL, CRP 3.6 mg/L, reticulocytes 2.8%, creatinine 0.77 mg/dL.

• Serum electrolytes: Sodium 140 mmol/L, Potassium 4.85 mmol/L, Urea 39.1 mg/dL.

• Abdominal radiograph: Massively dilated bowel loops with absent rectal gas.

• Ultrasound cranium: Persistent cavum septum pellucidum; no intraventricular hemorrhage.

• Levelling biopsies (colon, sigmoid, ileum, ileostomy site): Absence of ganglion cells in colon, sigmoid, and distal ileum; normal ganglion cells in proximal ileum — confirming total colonic aganglionosis.

• Chest X-ray (Day 9): Normal lung fields; no bowel gas under diaphragm.

• Repeat CBC on 29 Oct 2024: Hb 15.9 g/dL, WBC 12,800/µL, platelets 290 × 10^3/µL.

• Hearing screening and ophthalmic evaluation were deferred for outpatient follow-up.

5. MANAGEMENT

Management encompassed acute stabilisation, definitive surgical intervention, and long term multidisciplinary follow up.

Acute Stabilisation (Day 0–2)

• Airway & Breathing: Immediate oxygen via hood; hypercapnia treated with synchronized intermittent mandatory ventilation (SIMV) once pCO_2 > 60 mmHg.

• Circulation: Isotonic fluid bolus 10 mL/kg for initial dehydration; maintenance 100 mL/kg/day.

• Metabolic: 10 % dextrose infusion; serial blood gases and electrolytes every 6 h.

• Empiric antibiotics: Ciprofloxacin 20 mg/kg/day + Amikacin 15 mg/kg/day pending cultures.

• Glycaemic control: IV dextrose titrated to maintain serum glucose 70–110 mg/dL.

2. Gastrointestinal & Surgical Management

• Nasogastric decompression to prevent perforation.

• Levelling biopsies (rectum → ileum) performed within 48 h.

• Emergency laparotomy (Day 8): Total colonic aganglionosis recognised; loop ileostomy fashioned 25 cm proximal to ileocecal junction, preserving maximal small bowel.

• Post op stoma care: Colostomy bag change q 8 h; peristomal zinc oxide barrier.

• Definitive pull through (Duhamel retro rectal pouch) planned at 8–10 kg body weight.

3. Respiratory & Autonomic Management

• CCHS Protocol: Nocturnal BiPAP (inspiratory 16 cmH_2O, expiratory 6 cmH_2O) targeting $pCO_2 < 50$ mmHg.

• Apnea monitoring: Cardiorespiratory impedance monitor during sleep; home monitor loaned at discharge.

• Consideration for tracheostomy and diaphragm pacing if ventilator dependence persists beyond 6 months.

4. Nutritional & Metabolic Support

• Parenteral nutrition (80 kcal/kg/day) for first 72 h post op.

• Enteral feeds: Expressed breast milk started 20 mL/kg/day on POD 3; advanced 20 mL/kg/day.

• Micronutrient supplementation: Zinc 2 mg/kg/day, fat soluble vitamins, and medium chain triglyceride fortification once full feeds achieved.

• Stoma output replacement with equal volume isotonic fluid + 10 mmol/L KCl to prevent hyponatraemia.

5. Pharmacologic Adjuncts

• Analgesia: IV paracetamol 15 mg/kg q6h × 48 h; morphine avoided due to respiratory depression risk.

• Vitamin K 1 mg IM single dose.

• Pro kinetics (erythromycin 3 mg/kg q8h) temporarily for postoperative ileus.

6. Infection Prophylaxis & Immunisation

• Central line–associated infection prophylaxis with chlorhexidine impregnated dressings.

• Immunisation per National Immunisation Schedule; pneumococcal and RSV prophylaxis advised.

7. Multidisciplinary & Family Centred Care

• Specialists: Neonatology, Pediatric Surgery, Pulmonology, Genetics, Audiology, Ophthalmology, Physiotherapy.

• Parental education: Stoma management, signs of dehydration, use of home apnea monitor.

• Genetic counselling: Autosomal dominant PHOX2B with variable penetrance; WS gene testing advised for parents.

• Psychosocial support and linkage to rare disease support groups.

8. Long Term Surveillance

• Six monthly growth and developmental assessments (Bayley III).

• Annual auditory and ophthalmic evaluations due to WS risk of sensorineural deafness.

• Sleep polysomnography every 6 months to titrate ventilatory settings.

• Routine colonoscopy 1 year post pull through to assess for residual aganglionosis.

6. DISCUSSION

This case exemplifies the embryological convergence of pigmentary, enteric, and autonomic dysfunction in a single neonate, reinforcing the concept of neurocristopathy continua rather than discrete disorders. (6) The classification table underscores how apparently disparate conditions share a neural crest lineage. Early recognition of pigmentary cues expedited targeted histology and PHOX2B analysis, enabling anticipatory respiratory management before life threatening apneic crises

ensued.(7)The convergence of Waardenburg syndrome (WS), Hirschsprung disease (HD), and congenital central hypoventilation syndrome (CCHS) in this patient represents a rare triad of neurocristopathies affecting three distinct neural crest-derived systems—melanocytes, enteric neurons, and autonomic respiratory regulation. (8) While the coexistence of HD and WS (Waardenburg type IV or Shah-Waardenburg syndrome) is recognized, and the combination of HD and CCHS (Haddad syndrome) is well-described, the simultaneous manifestation of all three has not been reported in Indian literature and remains exceptionally rare worldwide. (9)Embryologically, neural crest cells migrate from the dorsal neural tube to various regions where they differentiate into multiple structures including the peripheral nervous system, melanocytes, craniofacial skeleton, and enteric ganglia. Disruptions in this finely coordinated process can result in multisystem involvement, as illustrated in this neonate. Genes like PHOX2B, EDNRB, EDN3, and SOX10 play pivotal roles in this migration and differentiation, and mutations in these genes are frequently associated with neurocristopathies. In this case, PHOX2B mutation confirmed the diagnosis of CCHS, while clinical markers were consistent with WS type IV. (10)The clinical presentation of delayed meconium passage, abdominal distension, and distinctive pigmentation anomalies, coupled with apnea and hypercapnia in early neonatal life, should prompt a high index of suspicion for a syndromic diagnosis. This case demonstrates the diagnostic value of integrating dermatological cues with gastrointestinal and respiratory findings in identifying syndromic aganglionosis.Management of such complex cases requires timely recognition, staged surgical correction, and a comprehensive, multidisciplinary approach. The early establishment of an ileostomy allowed decompression and nutritional support, while targeted ventilatory strategies helped stabilize autonomic function. Genetic counseling played a vital role, especially considering the consanguineous background and recurrence risk.The long-term prognosis of such patients remains guarded due to potential complications, including stoma-related issues, enterocolitis, ventilator dependence, and developmental delays. Regular follow-up with neurologists, pulmonologists, and developmental pediatricians is essential. Advances in genetic research and molecular diagnostics may help identify additional modifier genes that contribute to this unique phenotype, paving the way for more individualized therapeutic strategies. (11)Finally, this case underscores the importance of considering rare syndromic overlaps in neonates with complex presentations. Documenting and reporting such cases is crucial to enhancing our understanding of neurocristopathies and may lead to improved classification, earlier recognition, and better outcomes through multidisciplinary care.

7. CONCLUSION

Coexistence of Haddad and Waardenburg syndromes represents an extreme end of the neurocristopathy spectrum. Comprehensive management demands prompt multidisciplinary coordination, genotype phenotype correlation, and proactive family engagement. Reporting such overlaps enriches the global database, guiding clinicians facing similar perplexing neonatal presentations.

Acknowledgments

We thank the Departments of Neonatology, Pediatric Surgery, Pulmonology, Pathology, and Genetics at KLES Dr. Prabhakar Kore Hospital for their expertise and collaboration. Our gratitude extends to the patient's family for allowing this report.

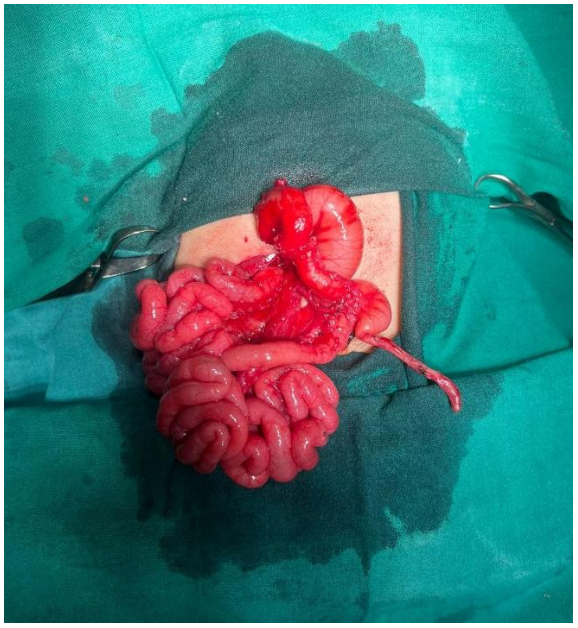

Figure 1: Intraoperative photograph showing exteriorized aganglionic colon and distended small bowel loops

during emergency laparotomy in a neonate with total colonic aganglionosis.

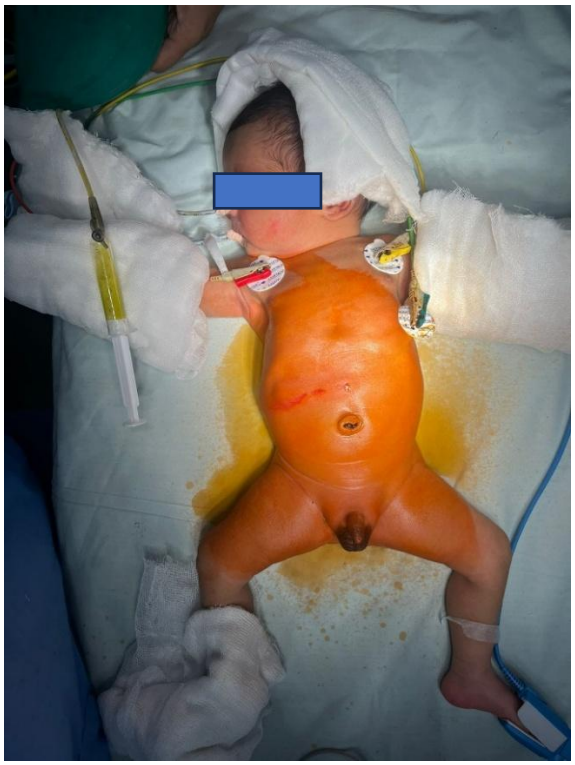

Figure 2: Preoperative clinical image of the neonate showing gross abdominal distension, jaundice, and nasogastric decompression in a case of total colonic aganglionosis with central hypoventilation (Haddad-Waardenburg overlap).

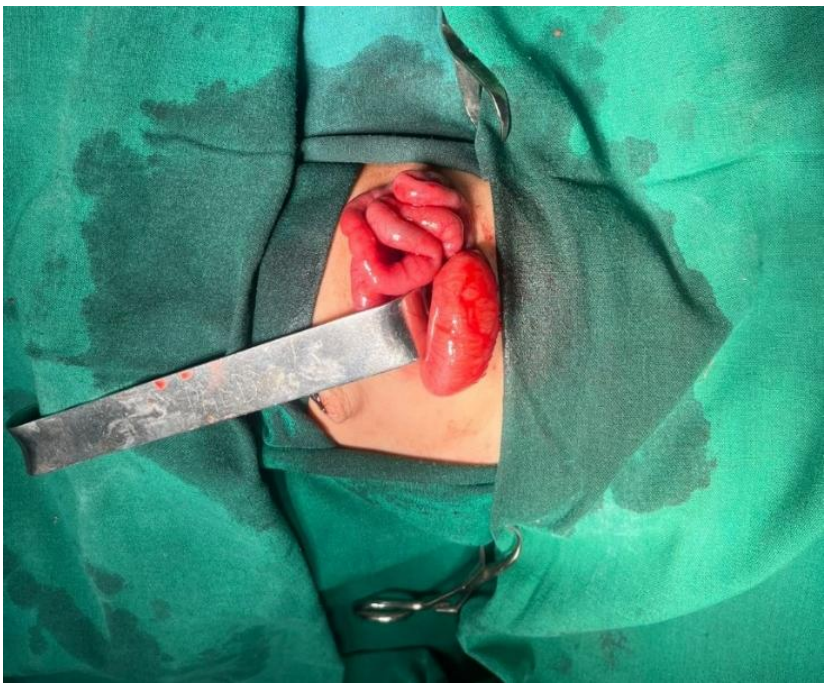

Figure 3: Intraoperative image demonstrating proximal transition zone and small bowel segment prior to stoma formation in a neonate diagnosed with total colonic aganglionosis.

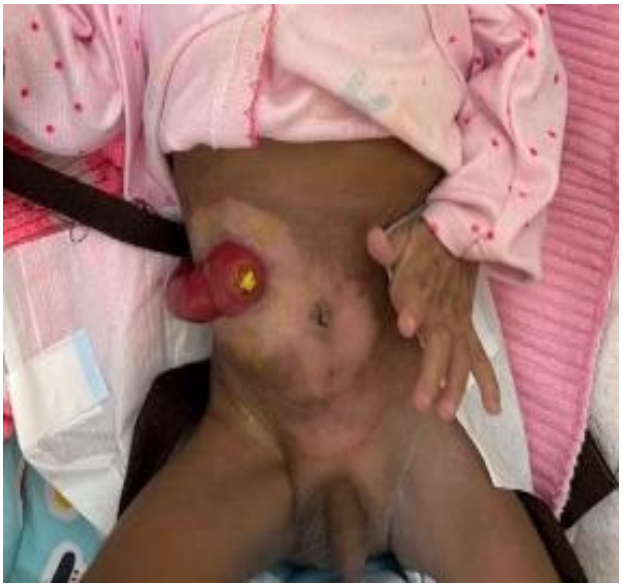

Figure 4: Follow-up image showing undernourished appearance, visible stoma, pigmentary abnormalities including white forelock and bright blue irides consistent with Waardenburg phenotype in a child with established diagnosis of Haddad-Waardenburg syndrome.

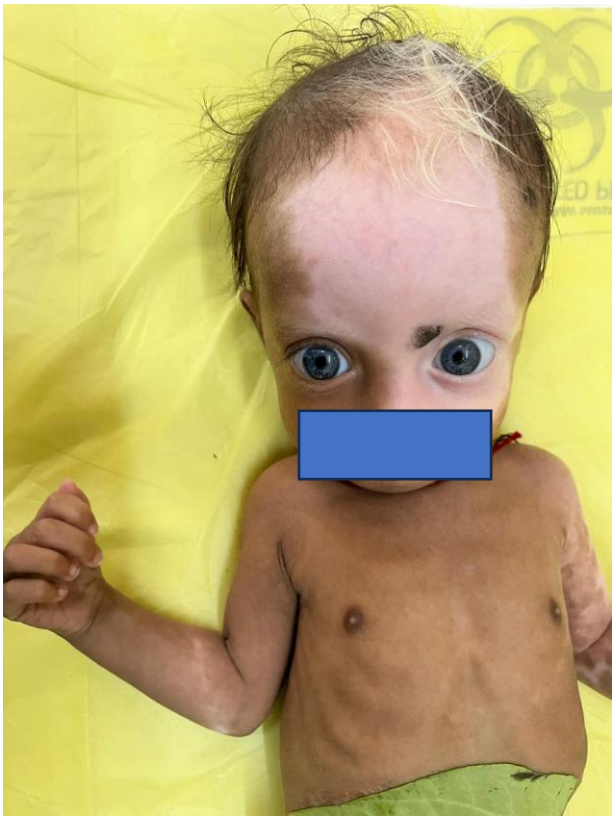

Figure 5: Close-up follow-up image highlighting hypopigmented patches, heterochromia with brilliant blue irides, and a depigmented frontal white forelock—classic features of Waardenburg syndrome in a child with confirmed Haddad-Waardenburg overlap.

REFERENCES

[1] Shahar E, Shinawi M. Neurocristopathies presenting with neurologic abnormalities associated with Hirschsprung's disease. Pediatr Neurol. 2003 May;28(5):385–91.

[2] Waardenburg Syndrome - StatPearls - NCBI Bookshelf [Internet]. [cited 2025 Jun 21]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560879/

[3] Trang H, Samuels M, Ceccherini I, Frerick M, Garcia-Teresa MA, Peters J, et al. Guidelines for diagnosis and management of congenital central hypoventilation syndrome. Orphanet J Rare Dis. 2020 Sep 21;15:252.

[4] Hogan AR, Rao KA, Thorson WL, Neville HL, Sola JE, Perez EA. Waardenburg Syndrome Type IV De Novo SOX10 Variant Causing Chronic Intestinal Pseudo-Obstruction. Pediatr Gastroenterol Hepatol Nutr. 2019 Sep;22(5):487–92.

[5] ResearchGate [Internet]. [cited 2025 Jun 21]. Table 1 The Neurocristopathies Classification. Available from: https://www.researchgate.net/figure/The-Neurocristopathies-Classification_tbl1_221722590

[6] Neurocristopathies | Embryo Project Encyclopedia [Internet]. [cited 2025 Jun 21]. Available from: https://embryo.asu.edu/pages/neurocristopathies

[7] Weese-Mayer DE, Rand CM, Khaytin I, Slattery SM, Yap KL, Marazita ML, et al. Congenital Central Hypoventilation Syndrome. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993 [cited 2025 Jun 21]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1427/

[8] Croaker G, Shi E, Simpson E, Cartmill T, Cass D. Congenital central hypoventilation syndrome and Hirschsprung's disease. Arch Dis Child. 1998 Apr;78(4):316–22.

[9] Khan TA, Safdar CA, Zameer S, Khushdil A. Waardenburg-Shah syndrome (WS type IV): a rare case from Pakistan. Perioper Med. 2020 Jan 24;9:4.

[10] Autonomic neurocristopathy-associated mutations in PHOX2B dysregulate Sox10 expression - PubMed [Internet]. [cited 2025 Jun 21]. Available from: https://pubmed.ncbi.nlm.nih.gov/22922260/

[11] Stanford A, Upperman JS, Boyle P, Schall L, Ojimba JI, Ford HR. Long-term follow-up of patients with necrotizing enterocolitis. J Pediatr Surg. 2002 Jul;37(7):1048–50; discussion 1048-1050.