Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Pediatric intestinal pseudo-obstruction in hypoparathyroidism-retardation-dysmorphism syndrome

Rotem Shalev Shamay
Rotemshal@gmail.com
Soroka University Medical Center
Borislava Kogan
Soroka University Medical Center
Gadi Howard
Soroka University Medical Center
Neta Loewenthal
Soroka University Medical Center
Hadas Cohavy Akiva
Soroka University Medical Center
Lidia Osyntsov
Soroka University Medical Center
Galina Ling
Soroka University Medical Center
Baruch Yerushalmi
Soroka University Medical Center

Research Article

Keywords: hypoparathyroidism-retardation-dysmorphism syndrome, pediatric intestinal pseudo-obstruction, TBCE, parenteral nutrition, intestinal failure, hypocalcemia

Posted Date: June 6th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9806249/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Pediatric intestinal pseudo-obstruction in hypoparathyroidism-retardation-dysmorphism syndrome

Rotem Shalev Shamay[1,4], Borislava Kogan[1,4] Gadi Howard [1,4], Neta Loewenthal [2,4], Hadas Cohavy Akiva[5], Lidia Osyntsov [3,4], Galina Ling [1,4], Baruch Yerushalmi [1,4]

[1] Pediatric Gastrointestinal Unit, Soroka University Medical Center, Beer Sheva, Israel

[2] Pediatric Endocrinology Unit, Soroka University Medical Center, Beer Sheva, Israel

[3] Pathology Institute, Soroka University Medical Center, Beer Sheva, Israel

[4] Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel

[5]Nutrition Unit, Soroka University Medical Center, Beer Sheva, Israel

Corresponding author:

Rotem Shalev Shamay, MD

Pediatric Gastroenterology Unit, Soroka University Medical Center

Beer Sheva, Israel

Email: Rotemsha@clalit.org

Tel: +972-8-6400624

Abstract

Pediatric intestinal pseudo-obstruction (PIPO) has been observed in patients with hypoparathyroidism-retardation-dysmorphism (HRD) syndrome, but its frequency, clinical burden, and potential mechanisms have not been systematically characterized. We aimed to evaluate PIPO and related morbidity in a large single-center cohort of children with HRD. We performed a retrospective cohort study and included all the pediatric patients with clinically and genetically confirmed HRD followed between 1990 and 2025. Demographic, clinical, radiological, pathological, and nutritional data were extracted from electronic medical records. Seventy-nine patients with HRD were identified; all were of Bedouin origin and carried the same founder *TBCE* mutation. Nineteen patients (24%) were diagnosed with PIPO. Among them, five (26.3%) required parenteral nutrition (PN). PIPO presented with the typical clinical and radiological findings. Patients requiring PN had substantial morbidity related to intestinal failure and central venous access. Three of the five PN-dependent patients died from severe infectious complications.

Conclusion: PIPO is a frequent and severe gastrointestinal complication of HRD syndrome. Early recognition, optimized nutritional management, and prevention of infectious complications are essential. *TBCE*-related neuromuscular dysfunction and recurrent hypocalcemia may both contribute to impaired intestinal motility.

Keywords: hypoparathyroidism-retardation-dysmorphism syndrome; pediatric intestinal pseudo-obstruction; *TBCE*; parenteral nutrition; intestinal failure; hypocalcemia

What is Known - What is New

What is Known:

HRD is a TBCE-related disorder with endocrine, neurodevelopmental, and immune involvement.

PIPO may lead to intestinal failure and need for parenteral nutrition.

What is New:

In 79 HRD patients, 24% had PIPO; five required PN, with high infectious morbidity/mortality.

PIPO in HRD may reflect hypocalcemia plus TBCE-related neuromuscular and cytoskeletal dysfunction.

Abbreviations

HRD, hypoparathyroidism-retardation-dysmorphism

IRB, institutional review board

PIPO, pediatric intestinal pseudo-obstruction

PN, parenteral nutrition

PTH, parathyroid hormone

SUMC, Soroka University Medical Center

Introduction

Hypoparathyroidism-retardation-dysmorphism (HRD) syndrome (OMIM #241410) is a rare autosomal recessive disorder reported predominantly among Arab populations in the Middle East. It shares clinical and genetic features with Sanjad-Sakati syndrome and Kenny-Caffey syndrome type 1 and results from mutations in the *TBCE* gene [1-3]. The syndrome is characterized by severe pre- and postnatal growth restriction, short stature, dysmorphic features, and hypoparathyroidism causing hypocalcemia, often accompanied by seizures and significant neurodevelopmental impairment.

HRD is a multisystem disorder. In addition to endocrine abnormalities, patients may have immunodeficiency and other endocrinopathies, including hypothyroidism, adrenal insufficiency, hypoglycemia, and hypogonadism [4]. Among the Bedouin population of the Negev region, a founder mutation, c.155_166delGCCACGAAGGG (p.Ser52_Gly55del), has been identified in the *TBCE* gene, with an estimated incidence of approximately 1 in 5,000 live births at Soroka University Medical Center (SUMC) [4].

The high mortality associated with HRD has been attributed largely to infectious complications related to the underlying immunodeficiency. Patients are particularly susceptible to severe bacterial infections, and daily prophylactic antibiotic therapy has been shown to reduce mortality [4]. No curative treatment currently exists; management is supportive and includes calcium supplementation, active vitamin D metabolites, prophylactic antibiotics, pneumococcal vaccination, and hormone replacement when indicated [5].

With improved supportive care and longer survival, gastrointestinal involvement in HRD has become increasingly recognized. Reported manifestations include prolonged neonatal cholestasis, recurrent gastrointestinal infections,

and later presentations of pediatric intestinal pseudo-obstruction (PIPO), but detailed characterization remains limited [4].

PIPO is a rare, severe gastrointestinal motility disorder that primarily affects the small intestine and colon and may lead to intestinal failure. In children with HRD, recurrent pseudo-obstruction may prevent adequate enteral nutrition and necessitate parenteral nutrition (PN), which carries substantial risks including intestinal failure-associated liver disease, central venous catheter-related thrombosis, and sepsis.

At the Saban Children's Hospital at SUMC, a large cohort of children of Bedouin origin with HRD is followed. Despite increasing recognition of the multisystem nature of HRD, data specifically addressing PIPO as a gastrointestinal complication remain scarce. This study aimed to evaluate and characterize PIPO and its associated morbidity in children with HRD syndrome.

Materials and methods

A population-based retrospective cohort study was conducted at SUMC. The study included pediatric patients (<=18 years of age) diagnosed with HRD syndrome, based on clinical and/or genetic criteria, between 1990 and 2025. Data were extracted from the hospital computerized medical records, including inpatient and outpatient databases, after institutional review board approval. Collected data included demographic and clinical characteristics, gastrointestinal-related emergency department visits, hospitalizations, pediatric intensive care unit admissions, and the need for PN.

Additional outpatient data included documented gastrointestinal diagnoses, prescribed treatments such as laxatives, elemental diets, hydrolyzed formulas or other specialized nutritional regimens, and relevant laboratory investigations performed at the hospital.

Patients with incomplete medical records were excluded from detailed clinical analyses.

Results

Seventy-nine patients with HRD syndrome were identified between 1990 and 2025. All were of Bedouin origin and carried the same mutation. Nineteen patients (24%) were diagnosed with PIPO. Among patients with PIPO, five (26.3%) required PN. Insufficient clinical documentation was noted in 7 of the 79 patients, and these patients were excluded from detailed analyses.

Clinical presentation of PIPO was characterized predominantly by progressive abdominal distension and recurrent bilious vomiting. Deterioration was often associated with intercurrent illnesses, including infections and metabolic disturbances such as hypocalcemia.

Among the 19 patients diagnosed with PIPO, the severity of disease varied. Detailed clinical and demographic characteristics of the five patients requiring PN are summarized in Table 1.

All patients requiring PN needed central venous access with a Hickman catheter, typically placed during late childhood. The age at catheter placement ranged from approximately 9.8 to 13.6 years. PN support ranged from 12 to 24 hours per day. Enteral feeding was limited or absent in most patients, although partial enteral intake was achieved in selected cases. All patients required adjunctive gastrointestinal treatments, including laxatives and enemas (Table 1).

Despite severe disease, patients receiving PN demonstrated substantial weight gain, supporting the role of targeted nutritional therapy. However, PN dependence was associated with major morbidity and mortality. Four of the five patients requiring PN died from severe infectious complications after a PN duration ranging from approximately 1 to 27 months, whereas one patient showed clinical improvement with partial PN support. An interesting observation during the PN administration was that lower phosphate concentrations in the PN formulation were associated with optimal biochemical control of serum calcium and phosphate levels without the need for alpha- D3 supplementation.

Radiological findings were consistent with intestinal pseudo-obstruction and included diffuse bowel dilatation, multiple air-fluid levels, and relative paucity of distal bowel gas, often mimicking mechanical obstruction (Fig. 1). In most cases, bowel dilatation was first documented during childhood, with age at first documented imaging ranging from 5 years 11 months to 12 years 11 months (Table 1).

One patient underwent extensive surgical intervention, including total colectomy. Gross examination of the resected specimen, including colon (107 cm), terminal ileum (3 cm), and appendix, demonstrated marked bowel dilatation without evidence of mechanical obstruction (Fig. 2). Histological analysis showed normal mucosal and submucosal architecture, preserved ganglion cells, and normal neural elements. In contrast, marked atrophy of both layers of the muscularis propria was identified, accompanied by fibrosis highlighted by Masson trichrome staining. Immunohistochemical staining demonstrated preserved smooth muscle actin and desmin expression in both muscle layers. Interstitial cells of Cajal were present by c-Kit immunostaining. No PAS-positive cytoplasmic inclusions were identified.

Discussion

This study identifies PIPO as a clinically important gastrointestinal complication of HRD syndrome. In this large single-center cohort, 24% of patients with HRD had PIPO, and more than one quarter of affected patients required PN.

The observed proportion of PIPO may underestimate the true burden of disease because of survivorship bias. Historically, many patients with HRD died during the first decade of life from infectious complications and may not have survived long enough for late-onset pseudo-obstruction to become clinically evident. With improved supportive care and longer survival, PIPO may emerge as a more prominent contributor to morbidity.

The pathophysiology of PIPO in HRD is probably multifactorial. Recurrent hypocalcemia due to hypoparathyroidism may impair smooth muscle contraction and coordinated intestinal peristalsis. However, metabolic disturbances alone are unlikely to explain the severity and persistence of the disorder. *TBCE* encodes a tubulin-specific chaperone required for alpha-tubulin folding, heterodimerization with beta-tubulin, and microtubule assembly [2]. Because microtubules are essential for intracellular transport, neuronal integrity, and cellular organization, *TBCE* dysfunction may impair enteric neuronal and smooth muscle function. Experimental data supporting a critical role for *TBCE* and microtubule assembly in neuronal maintenance further support this hypothesis [6, 7].

Pathological findings in our cohort support a neuromuscular mechanism. Preserved enteric ganglia were identified despite marked muscularis propria atrophy and fibrosis, suggesting a primary myopathic component, although combined neurogenic and myopathic dysfunction remains plausible. In addition, cytoskeletal disruption may affect intestinal epithelial homeostasis, including enterocyte proliferation, differentiation, cell-cell and cell-matrix interactions, intracellular trafficking, and apicobasal polarity [8]. These mechanisms may further aggravate impaired intestinal function.

Clinically, severe PIPO frequently led to intestinal failure and long-term PN. The high mortality among PN-dependent patients in this cohort is consistent with reported outcomes in intestinal pseudo-obstruction, where morbidity and death are often related to complications of intestinal failure and PN, particularly catheter-related infections [9].

The strengths of this study include a large, well-characterized HRD cohort from a tertiary center with extensive experience in this rare disorder, and the integration of clinical, radiological, pathological, and mechanistic

observations. Limitations include the retrospective design, incomplete documentation for some patients, the single-population setting, and the absence of direct functional studies. Therefore, proposed mechanisms should be considered hypothesis-generating.

Conclusions

PIPO is a frequent and severe complication of HRD syndrome and a major contributor to morbidity and mortality. Its development may reflect an interplay between recurrent hypocalcemia, *TBCE*-related microtubule dysfunction, neuromuscular impairment, and altered epithelial homeostasis. Early recognition, optimized nutritional support, and prevention of catheter-related infections are essential. Further studies are needed to define the relative contribution of metabolic, neurogenic, myopathic, and epithelial mechanisms and to guide targeted therapies.

References

1. Parvari R, Hershkovitz E, Grossman N, Gorodischer R, Loeys B, Zecic A, Mortier G, Gregory S, Sharony R, Kambouris M et al (2002) Mutation of *TBCE* causes hypoparathyroidism-retardation-dysmorphism and autosomal recessive Kenny-Caffey syndrome. Nat Genet 32:448-452. https://doi.org/10.1038/ng1012

2. Hershkovitz E, Parvari R, Diaz GA, Gorodischer R (2004) Hypoparathyroidism-retardation-dysmorphism (HRD) syndrome - a review. J Pediatr Endocrinol Metab 17:1583-1590

3. David O, Kristal E, Ling G, Broides A, Hadad N, Shubinsky G (2023) Hypoparathyroidism retardation dysmorphism syndrome due to a variant in the tubulin specific chaperone E gene as a cause of combined immune deficiency. J Clin Immunol 43:350-357

4. David O, Agur R, Novoa R, Shaki D, Walker D, Carmon L, Eskin-Schwartz M, Birk OS, Ling G, Schreiber R et al (2022) Hypoparathyroidism-retardation-dysmorphism syndrome-clinical insights from a large longitudinal cohort in a single medical center. Front Pediatr. Published 22 July 2022

5. Hershkovitz E, Rozin I, Limony Y, Golan H, Hadad N, Gorodischer R, Levy R (2007) Hypoparathyroidism, retardation, and dysmorphism syndrome: impaired early growth and increased susceptibility to severe infections due to hyposplenism and impaired polymorphonuclear cell functions. Pediatr Res 62:505-509

6. Schaefer MK, Schmalbruch H, Buhler E, Lopez C, Martin N, Guenet JL, Haase G (2007) Progressive motor neuronopathy: a critical role of the tubulin chaperone *TBCE* in axonal tubulin routing from the Golgi apparatus. J Neurosci 27:8779-8789

7. Fujiwara H, Watanabe S, Iwata M, Ueda S, Nobuhara M, Wada-Kakuda S, Misonou H, Miyasaka T (2020) Inhibition of microtubule assembly competent tubulin synthesis leads to accumulation of phosphorylated tau in neuronal cell bodies. Biochem Biophys Res Commun 521:779-785

8. Perrin L, Matic Vignjevic D (2023) The emerging roles of the cytoskeleton in intestinal epithelium homeostasis. Semin Cell Dev Biol 150-151:23-27

9. Mousa H, Hyman PE, Cocjin J, Flores AF, Di Lorenzo C (2002) Long-term outcome of congenital intestinal pseudoobstruction. Dig Dis Sci 47:2298-2305

Statements and Declarations

Funding: The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Competing interests: The authors have no relevant financial or non-financial interests to disclose.

Author contributions: Rotem Shalev Shamay, Borislava Kogan, and Baruch Yerushalmi contributed to the study conception and design. Data collection and analysis were performed by Rotem Shalev Shamay, Borislava Kogan, Gadi Howard, Neta Loewenthal, Evelin Farkash Novik, Lidia Osyntsov, and Galina Ling. The first draft of the manuscript was written by Rotem Shalev Shamay, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Soroka University Medical Center Institutional Review Board (approval number: [insert IRB/Helsinki approval number]).

Consent to participate: The requirement for informed consent was waived by the institutional review board because of the retrospective design.

Consent to publish: Not applicable.

Data availability: The datasets generated and/or analyzed during the current study are not publicly available because they contain patient-level clinical data, but de-identified data may be available from the corresponding author on reasonable request and subject to institutional approvals.

Table 1 Clinical and demographic characteristics of patients with HRD-related PIPO requiring parenteral nutrition

	Case 1	Case 2	Case 3	Case 4	Case 5
Date of birth	16/10/2010	15/02/2010	16/08/2010	19/02/2010	31/10/2014
Gender	female	female	male	female	female
Birth weight (Kg)	2.34	1.622	2.27	2.012	1.810
First X-Ray showing dilated bowel loops	18/06/2017	22/08/2019	07/08/2023	16/12/2022	21/10/2020
Age	6 years, 8 months	9 years, 6 months	12 years, 11 months	12 years, 9 months	5 years, 11 months
Cause of the deterioration	lung disease	Sepsis	hypocalcemia and vomiting	sepsis- strep. Pneumonia	hypocalcemia and vomiting
Central venous access (Hickman)	08/04/2024	28/08/2023	29/01/2024	09/01/2023	17/09/2024
Age at central venous access (years)	13 years, 5 months	13 years, 6 months	13 years, 5 months	12 years, 10 months	9 years, 10 months
Hours of TPN support/ Day	24	24	12	14	20
Additional GI treatment	Enema, PEG3350	Enema, PEG3350	Enema, PEG3350	Enema, PEG3350	Enema, PEG3350
Enteral feeding	none	none	Nutren, 50 ml x 6/day	soft and liquid intake	none
Surgery		28/07/2023- colectomy 09/08/2023- laparoscopic band removal, gastrostomy 10/8/2023- stoma malfunction			
Date of death	25/04/2024	26/09/2023		04/04/2025	
Age on death (years)	13 years, 6 months	13 years, 7 months		15 years, 1 month	

Figure legends

Fig. 1 Abdominal radiographs from a patient with HRD-related PIPO demonstrating diffuse bowel dilatation and multiple air-fluid levels with paucity of distal bowel gas

Fig. 2 Gross total colectomy specimen demonstrating marked bowel dilatation without mechanical obstruction

Figures

Fig. 1



241 Fig. 2



242