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Case Report
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Familial Hypoganglionosis Presenting as Maternal Chronic Intestinal Dysmotility with Co-Occurring Subacute Combined Degeneration and Severe Anemia, and Acute Intussusception in Her Infant Daughter: A Two-Generation Case Series

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Abstract

We describe a mother–infant dyad. The mother, a 16-year-old teenager, presented with a background of lifelong chronic constipation, recurrent abdominal discomforts, pain and distension, and malabsorption. The patient presented suddenly with progressive gait disturbance, and profound anemia. She was diagnosed with hypoganglionosis on full-thickness biopsy and SCD on MRI. Her infant daughter presented at 7 months with acute ileocolic intussusception, requiring radiological reduction. Both cases occurred in the absence of known syndromic associations.

Keywords: Intestinal Hypoganglionosis; Enteric Neuropathy; Familial Gastrointestinal Dysmotility; Subacute Combined Degeneration; Vitamin B12 Deficiency Neuropathy; Severe Anemia; Maternal Malabsorption; Infantile Intussusception; Ileocolic Intussusception; Neuro-Gastrointestinal Disorders; Hereditary Enteric Nervous System Disorders; Two-Generation Case Series; First Reported Association

Introduction

Intestinal hypoganglionosis is a rare enteric neuropathy typically presenting in infancy or childhood, accounting for approximately 5% of non-Hirschsprung congenital innervation disorders [1-2]. Both congenital and acquired forms have been described, with diagnosis requiring full-thickness biopsy demonstrating reduced myenteric ganglion cells [3].

Subacute combined degeneration (SCD) is a neurological manifestation of vitamin B12 deficiency, characterised by dorsal column demyelination and progressive gait disturbance [4].

Case Presentation

Case 1: Mother

A teenage girl aged 16 years with background of progressive chronic constipation requiring frequent laxatives since childhood, recurrent abdominal pain, early satiety, suddenly started having symptoms of pallor, severe fatigue, paresthesia of glove and stockings distribution and gait instability. There was no relevant family history, no known congenital gastrointestinal disorders; no Hirschsprung disease; and no autoimmune disease.

Over the preceding 18 months, she developed marked abdominal bloating, episodic colicky pain, unintentional weight loss with failure to thrive, progressive numbness in lower limbs and hands, difficulty walking, with a broad-based gait and severe fatigue and exertional dyspnea. Patient was initially seen in the regional children hospital and referred to tertiary care university teaching hospital at Ahmedabad.

She required admissions twice for recurrent abdominal pain but diagnosed with nonspecific

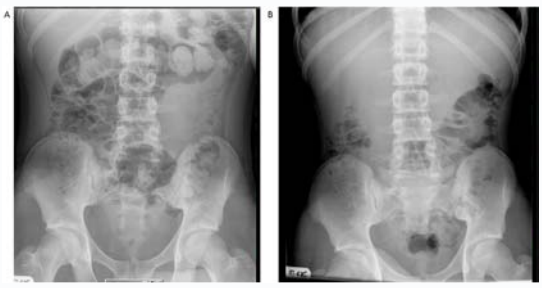

Figure 1: Mother-Abdominal radiographs A. At presentation B. After enema therapy.
Note dilated megarectum and massively dilated and fecal and gas loaded redundant colon and few characterless loops in the right side of the abdomen suggestive of ileocecal reflux in negative contrast.

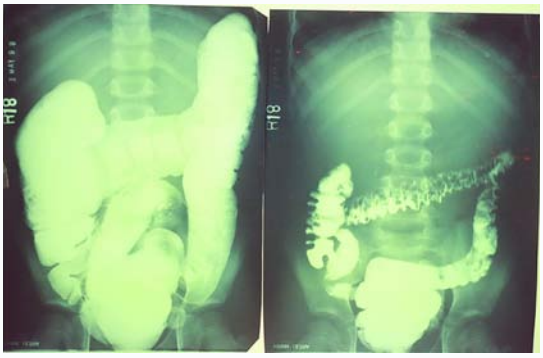

Figure 2: Mother-Lower Gastrointestinal contrast A. Filling phase B. Delayed film.
Note the filling phase showing transition at lower rectum with massively dilated megarectum and redundant colon, with massive ileocecal reflux. The delayed film shows retention of contrast in the terminal ileum from the ileocecal reflux and whole of the colon with dilated megarectum and transition in lower rectum.

pain secondary to chronic constipation treated with iron supplements for brief period for anemia.

Examination revealed very pale, fatigued, tachycardic vital signs. Abdominal examination showed distended, tympanic, sluggish bowel sounds with rectosigmoid loading. Neurological examination confirmed loss of vibration and proprioception in lower limbs, positive Romberg sign, spastic paraparesis and hyperreflexia.

Investigations

Laboratory investigations showed hemoglobin: 4.2 g/dL, MCV: macrocytic and anisocytosis, vitamin B12 severely reduced, folate normal, and iron studies provided with mixed picture consistent with chronic disease and malabsorption. Autoimmune screen was negative.

Imaging included abdominal plain radiography which showed gross fecal and gaseous loading of colon (Figure1). Gastrointestinal evaluation with lower gastrointestinal contrast enema showed massively loaded and dilated colon with transition zone in distal rectum and severe free ileocecal reflux (Figure 2). Anorectal manometry demonstrated markedly reduced rectoanal inhibitory reflex. Colonic transit study showed severe global delay. Hypoganglionosis was provisional diagnosis.

MRI spine depicted classical dorsal column hyperintensity ("inverted V sign") consistent with subacute combined degeneration.

Differential diagnosis included Hirschsprung disease (excluded by presence of ganglion cells), Chronic intestinal pseudo-obstruction, Autoimmune enteric neuropathy, Mitochondrial neuro-gastrointestinal disorders, Nutritional neuropathy (co-existing but not causative of dysmotility).

Treatment started with multidisciplinary team consisting of pediatric, pediatric gastroenterology, hematology-oncology, and neurology teams. Vitamin B12 replacement started parenterally. Blood transfusions with four units of packed cell for symptomatic anemia, high-calorie nutritional support, bowel regimen with osmotic laxatives and prokinetics.

Outcome and Follow-up

Neurological symptoms improved significantly after B12 therapy. Anemia stabilized without further transfusions. Gastrointestinal symptoms persisted but improved with structured bowel regimen. All four teams had no definitive unifying diagnosis and honestly told patient and parents that they do not know exactly what has caused these problems, all four teams will present the case to their annual conference to find out from brainstorming with some hints about it and requested to continue vitamin B12 injections every month and review in three months' time.

In the meantime, we have been inaugurating our PGICHR head office shift from Jamnagar to Rajkot on permanent basis and the patient residence was in our neighbourhood. The grandmother attended it and at the end she requested whether she can bring her granddaughter for injections every month for three months and having no background of her granddaughter's problems, a general comment was made that it is usually a lifelong course and we have an answer to reverse it as an authority with experience and authority but initially may prescribe for further evaluation.

At three months follow up, patient was requested to continue for 6 months and at six months for 1 year and at 1 year told her to continue life long as nobody at the conferences was able to figure out about the underlying cause so symptomatic treatment needs to continue. The grandmother brought her parents, and we discussed possibility of colorectal disorder with ileocecal reflux causing multiple micronutrient deficiencies which can explain both the acute presentations.

Consideration of surgical management (transanal endosurgical extended modified myomectomy) deferred for couple of months pending standard 12th Higher secondary A level examination. In the meantime, enema therapy started as conservative treatment to demonstrate that it worked well without any need for vitamin B12 supplements. She underwent the definitive surgical procedure after her examination uneventfully.

Definitive diagnosis established with the full-thickness rectosigmoid biopsy taken as part of the extended modified anorectal myomectomy. It demonstrated markedly reduced density of myenteric ganglion cells, small, immature ganglia, and hypertrophied nerve fibres consistent with intestinal hypoganglionosis. Genetic counselling was started at a later time because of the infant's subsequent presentation.

Case 2: Infant Daughter

After completing her university graduate and postgraduate studies index patient got married and had lovely Babygirl. A 7-month female infant and daughter of the above index patient in Case 1 was

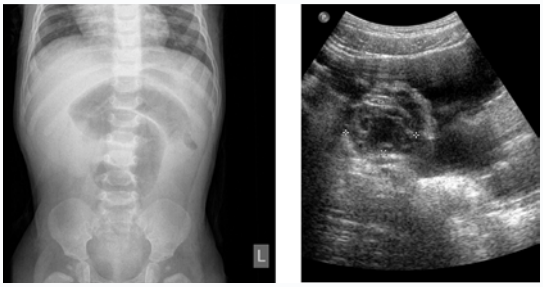

Figure 3: Babygirl-Imaging at presentation A. Abdominal radiograph B Ultrasound.
Note the intestinal obstruction pattern in the dilated air filled dilated characterless loops lower central abdomen and in the proximal jejunal loops and soft tissue shadow in right side of the abdomen with no gas in right iliac fossa. Ultrasound shows classic target sign with bowel within the bowel appearance.

born at term, after normal pregnancy scans and vaginal delivery with no neonatal complications. The meconium and urine passed soon after birth in the first 24 hours and had been passing regularly since then. Baby was breastfed with normal growth trajectory. Baby had infantile colic from 3 to 6 weeks at which time started having chronic constipation. Family history included mother with hypoganglionosis, symptomatic severe anemia, and SCD (Case 1).

Acute onset sudden inconsolable crying, drawing up of legs, intermittent abdominal pain and one episode of "red-currant jelly" stool. Abdominal radiograph showed obstructive pattern and referred to us (Figure 3A).

Examination showed her to be pale but alert with an abdominal tenderness in right lower quadrant, a palpable mass and no peritonism.

Investigations

Ultrasound abdomen clearly showed a Target sign consistent with ileocolic intussusception (Figure 3B).

Laboratory investigations revealed normal hemoglobin and complete blood count, normal electrolytes, and no evidence of infection.

Management included immediate air enema reduction performed successfully, no surgical intervention required (Figure 4). However, air enema reduction radiological imaging did show evidence of hypoganglionosis. Observed for 24 hours and no recurrence.

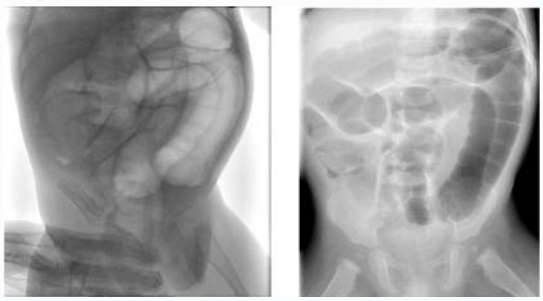

Figure 4: Babygirl-Pneumatic air enema reduction. A. In progress B. At completion.
Note the transition at the lower rectum in the A film and no rectal gas with retained gas in the dilated proximal colon and observations of other features of hypoganglionosis during the reduction procedure.

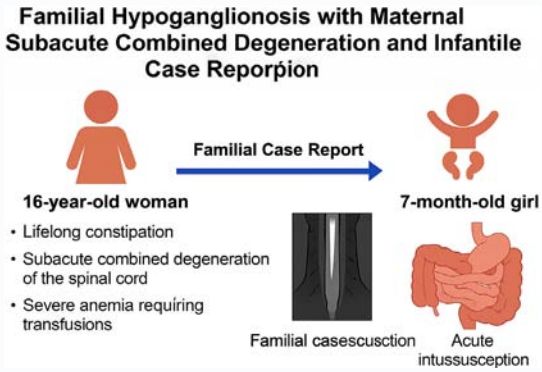

Figure 5: Graphical abstract illustrating a familial case series of hypoganglionosis and neurohematogastrointestinal complications.
The left panel depicts a sixteen-year-old girl (mother) with lifelong constipation, subacute combined degeneration of the spinal cord (MRI illustration), and severe anemia requiring transfusions. The right panel shows her seven-month-old daughter presenting with acute ileocolic intussusception (intestinal telescoping illustration). A horizontal arrow labelled "Familial Case Report" highlights the two-generation link. The abstract emphasizes the novel co-occurrence of enteric neuropathy, neurohematological complications, and infantile gastrointestinal emergency in a familial context.

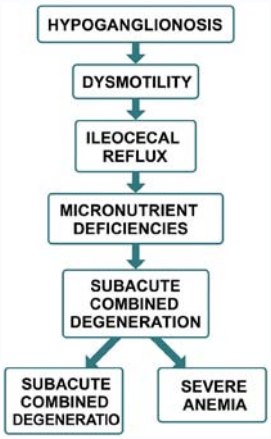

Figure 6: Pathophysiological cascade linking hypoganglionosis to neuro-hematological complications.
This schematic illustrates the proposed sequence of events in a patient with intestinal hypoganglionosis. The primary enteric neuropathy leads to severe colonic dysmotility, resulting in fecal and gas retention. This stagnant environment promotes dysbiosis and ileocecal reflux, impairing nutrient absorption and contributing to multiple micronutrient deficiencies. These deficiencies culminate in subacute combined degeneration of the spinal cord and severe transfusion-requiring anemia. The diagram highlights the interconnected gastrointestinal, microbial, nutritional, and neurological consequences of hypoganglionosis.

Outcome showed full recovery with normal feeding and bowel habits. Gastrointestinal symptoms persisted but improved with structured bowel regimen. However, patient continued to be having chronic constipated despite treatment. Referred for long-term follow-up due to maternal diagnosis and parents preferred to undergo definitive transanal endosurgical correction with extended modified anorectal myomectomy at the age of 18 months successfully. Full thickness rectal wall biopsy confirmed the hypoganglionosis. Long term follow up after 20 years showed both mother and the girl asymptomatic, well, and having no concerns.

Discussion

Intestinal hypoganglionosis is a rare enteric neuropathy typically

presenting in infancy or childhood. Adult-onset or familial forms are exceptionally uncommon. Co-occurrence with subacute combined degeneration (SCD) of the spinal cord and severe anemia requiring transfusion has not previously been described. Likewise, the presentation of acute intussusception in a first-degree relative raises the possibility of a shared genetic or developmental vulnerability of the enteric nervous system. Case reports detailing a presentation of familial hypoganglionosis with the co-occurrence of subacute combined degeneration of the spinal cord (SCD), severe anemia requiring blood transfusions, and acute intussusception in a baby girl do not appear in the available medical literature.

Intussusception is the most common abdominal emergency in infants, typically presenting between 4–9 months of age, with classical symptoms often absent in younger infants [1-3].

Familial clustering of enteric neuropathies has been increasingly recognised, with several susceptibility genes implicated in gut dysmotility syndromes [5-6].

To our knowledge, this is the first reported familial case series linking maternal hypoganglionosis with SCD and severe anemia, and infantile acute intussusception.

This two-generation case series highlights a possible shared enteric developmental vulnerability [7-8]. Familial enteric neuropathies have been associated with several genetic mechanisms affecting neuronal migration, interstitial cells of Cajal, and smooth muscle function [9-10].

The mother's severe dysmotility and the infant's intussusception may represent differing phenotypic expressions of an underlying enteric neuromuscular susceptibility.

This case series describes a unique familial presentation involving:

- A 16-year-old mother with biopsy-confirmed intestinal hypoganglionosis, complicated by subacute combined degeneration of the spinal cord and severe transfusion-requiring anemia, and
- Her 7-month-old daughter, who presented with acute ileocolic intussusception.

To our knowledge, this is the first reported two-generation cluster linking an enteric neuropathy with neuro-hematological complications in the mother and an acute gastrointestinal emergency in the infant. The report expands the phenotypic spectrum of familial enteric neuromuscular disorders and underscores the importance of considering subtle hereditary patterns in gastrointestinal dysmotility and infantile abdominal emergencies.

In our patient, hypoganglionosis led to profound colonic dysmotility with fecal and gas retention, creating a stagnant luminal environment favouring dysbiosis and SIBO-like physiology. This, in turn, promoted ileocecal reflux and colonisation of the distal small bowel by colonic flora, impairing absorption of key micronutrients, including vitamin B12 and iron. The resulting multi-micronutrient deficiency provided a unifying explanation for the coexistence of subacute combined degeneration of the spinal cord and severe transfusion-requiring anemia, thereby linking a primary enteric neuropathy to both neuro-logical and hematological manifestations.

This case series represents the first documented familial cluster linking:

1. Maternal intestinal hypoganglionosis
2. Maternal subacute combined degeneration
3. Maternal severe anemia requiring transfusion
4. Infantile acute intussusception

Novelty

- Hypoganglionosis is rare; familial patterns are extremely uncommon.
- Co-occurrence with SCD has not been previously reported.
- Infantile intussusception in a first-degree relative raises the possibility of shared enteric developmental vulnerability, even if transient or subclinical.

Possible shared mechanisms

- Subtle genetic variants affecting enteric neural crest migration
- Maternal malabsorption contributing to fetal micronutrient deficiency
- Epigenetic influences on enteric neuronal development

Clinical implications

- Adults with lifelong constipation and unexplained dysmotility warrant evaluation for hypoganglionosis.
- Neurological symptoms in such patients should prompt assessment for nutritional deficiencies.
- Infants of affected mothers may benefit from early gastrointestinal surveillance

Learning Points

- Hypoganglionosis can present in adulthood with severe dysmotility and may coexist with neuro-hematological complications.
- Subacute combined degeneration may mask or exacerbate underlying gastrointestinal neuropathies.
- Familial clustering of enteric disorders, even with differing phenotypes (hypoganglionosis vs. intussusception), should prompt genetic consideration.
- Early recognition and multidisciplinary management improve outcomes for both mother and child.
- Genetic counselling is an integral component of care for affected families.

Conclusion

This is the first reported familial cluster linking maternal hypoganglionosis with pediatric gastro-neuro-hematological complications and infantile intussusception. The series highlights the need to consider subtle hereditary enteric neuropathies in atypical gastrointestinal presentations across generations. This two-generation case series documents a uniquely complex familial presentation linking maternal intestinal hypoganglionosis, subacute combined degeneration, and severe anemia with infantile acute intussusception—a constellation not previously described in the literature. The mother's adolescent onset of profound gastrointestinal dysmotility, compounded by neuro-hematological manifestations, underscores the need for heightened clinical suspicion of enteric neuropathies beyond early childhood. The infant's acute

intussusception, although common in paediatrics, gains additional significance when viewed through the lens of a possible shared developmental or genetic vulnerability of the enteric nervous system.

Together, these cases highlight the importance of considering familial patterns of gastrointestinal dysfunction, even when phenotypes differ markedly across generations. Early recognition, multidisciplinary evaluation, and longitudinal follow-up are essential to optimise outcomes and to deepen our understanding of rare enteric neuromuscular disorders. This report expands the clinical spectrum of familial enteric neuropathies and invites further exploration into their genetic and developmental underpinnings.

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