CASE REPORT

An Infant with Cachexia and Immature Ganglionic Colon: A Case Report of Highlighting Successful Patient Management with an Innovative Bowel Training Adaptation Program

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Background: Immature ganglionic colon is best characterized and defined as a variant form of Hirschsprung disease according to the diagnostic criteria from the Japanese Study Group of allied disorders of Hirschsprung disease proposed in 2015. In a systematic appraisal of recent guidelines (2022), insufficient information and guidance exists regarding the best practice management of such patients.

Case Report: A 3-month-old female in-vitro fertilized monozygotic twin born at 30 weeks' gestation with birthweight of 1,162 grams was referred to a university pediatric surgical center with cachexia and gross abdominal distension and later found to have biopsy-proven immature ganglionic colon. Utilizing a Santulli stoma, the infant's gut was repeatedly challenged with an individualized bowel training program resulting in full functional recovery crucially avoiding a permanent stoma and/or resectional pull through operation, which is a definitive surgical procedure for Hirschsprung disease.

Conclusion: The present case report highlights pertinent clinical features that may help guide timing of re-biopsy, showing crucially that intestinal ganglion cells can mature, and the pivotal and key collaborative role of pathology services can help guide definitive practice management aided by bowel training.

Keywords: Hirschsprung disease; Immature ganglion cell innervation; Intestinal malfunction; Santulli stoma

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Immature ganglionic colon (IMC) is best defined as a Hirschsprung disease (HD) variant disorder[1,2], first described by Spencer in 1966[3]. Current criteria for working diagnosis were proposed by the Japanese Study Group of allied disorders of HD in 2015[4]. The incidence covered by a recent survey is estimated at one to two patients per million live births[4].

In a recent review of guidelines, no one has fully considered the individual subtype(s) or peculiar variants of HD that do exist to help guide best practice management[5]. There are no specific index cases harboring IMC that have been reported as patient subject(s) showing spontaneous improvement[3,6]. Debated issues about pathological diagnosis include the reliability of intraoperative frozen section, precise identification of maturation stage, and morphology of ganglion cells, all dependent on the pathologists' experience and quality sampling reporting of analyzed specimens[7-9]. Functional intestinal recovery in this infant case report was achieved by utilizing purse-string closure of a Santulli diverting stoma that allowed intestinal peristalsis to evolve and progress with stooling in an antegrade manner to the anus. This innovative strategy care plan helped obviate multiple intestinal re-biopsy procedures with the patient and other major invasive therapies notably a resectional pull through Hirschsprung operation.

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Case Report

A 3-month-old girl, body weight 2,230 grams with cachexia and gross abdominal distension, was referred to a university pediatric surgery center in Bangkok, Thailand with a tentative working diagnosis

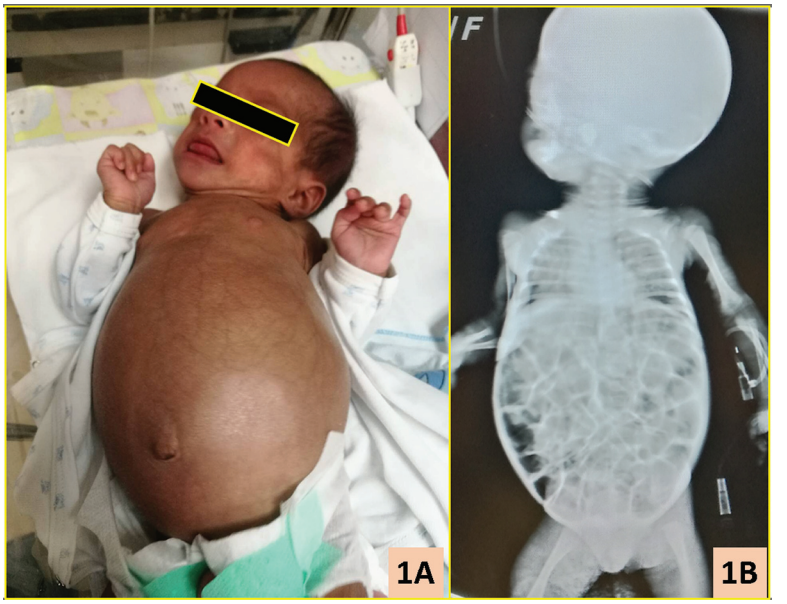

Figure 1. A 3-month-old female infant weight 2.23 kg presented with cachexia and gross abdominal distension (A). Plain abdominal X-ray film shows widespread intestinal tract dilatation (B).

of ultrashort segment Hirschsprung disease (USHD) (Figure 1A).

The present infant female, a 30-week gestation 1,162 grams in-vitro-fertilized monozygotic twin, was born from a 40-year-old non-diabetic mother by cesarean delivery due to premature rupture of membranes (PROM). The newborn was medically treated for an apnea of extreme prematurity for two months. Congenital hypothyroidism was treated with l-thyroxine at the age of one month. Neonatal sepsis from PROM, congenital pneumonia and fungal meningitis required multiple courses of antibiotics and anti-fungal therapy. At three months, she developed progressive gross abdominal distension after enteral feeding without confirmatory documentation on first-lifetime meconium passage and/or documentation of having necrotizing enterocolitis (NEC) illness even though the infant had been catheterized with a trans-umbilical vein and artery line for four and ten days in her early life, respectively. All plain abdominal X-ray films before full feeding had allegedly shown a normal intestinal gas pattern. The first X-ray film then confirming progressive intestinal dilatation and abdominal distension was at the age of three months (Figure 1B). The baby underwent a contrast enema examination that reported the possibility of USHD (Figure 2A) and a second enema study by a university pediatric radiology service stated suspicion of total colonic aganglionosis (TCA) (Figure 2B). With efforts to steadily improve nutritional status, the infant later was observed to pass soft yellow stools intermittently every few days. However, marked abdominal distension proved recurrent and troublesome after repeated oral feeding. Showing an atypical clinical course for USHD or classic HD, other potential causes of recurrent abdominal distension such as cow's milk allergy, adhesive bowel obstruction from undiagnosed medical NEC, or variant HDs were then considered. Serum levels of immunoglobulin E for cows' milk and post-treatment thyroid function tests, or euthyroid, ruled out these potential medical problems.

Levelling bowel biopsies were then scheduled after graded improvement in nutritional status. Rectal biopsy taken 2 cm above the dentate line revealed no ganglion cells in the submucosal and myenteric plexus with undefined hypertrophic nerve fibers. Laparoscopic serial biopsies of the appendix and ileum taken at 5 and 10 cm proximal to the ileocecal junction were inconclusive regarding the quality of ganglion cells or nerve plexuses on frozen section. A loop ileostomy was performed pending the final histopathology results on the quality of ganglion cells and management was then aimed at establishing a nutritional care plan at home. A Santulli ileostomy substituted the prolapsed ileostomy four months later, which she was then aged seven months. Intestinal effluent content was thus allowed to pass into the distal gastrointestinal tract as a trial effort for bowel transit and functional testing (Figure 3A, 3B). At

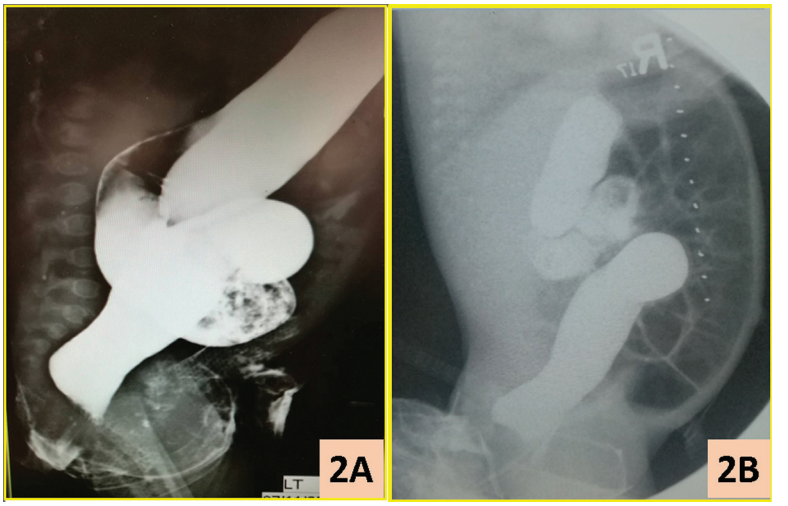

Figure 2. Contrast enema - 1st study taken at age 3 months reported ultrashort segment Hirschsprung disease (A). A follow-up contrast enema study at the referral hospital reported suspected total colonic aganglionosis (TCA) (B).

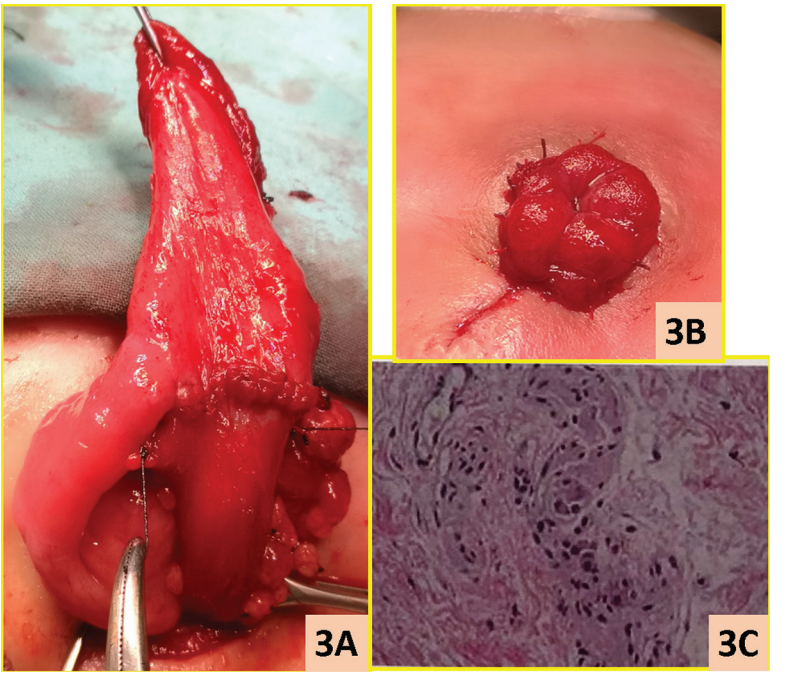

Figure 3. Prolapsed loop ileostomy corrected to a Santulli ileostomy for further intestinal function testing at 7-month-old (A-B). Microscopy showing scattered mature and immature ganglion cells in Auerbach and Meissner plexuses without identifiable neural hypertrophy (C).

the same Santulli stoma operation, re-biopsies of the rectum, sigmoid colon including both ends of the ileostomy were additionally sent to the pathology laboratory services for a second expert opinion. Pathologists from two independent laboratories reported all colonic specimens with the same results, notably scattered mature and immature ganglion cells observed in Meissner and Auerbach plexuses without evidence of neural hypertrophy (Figure 3C). A few ganglion cells in the rectum stained positively with Calretinin. Periodic testing at home, by closing the ileostomy with a temporary occlusive dressing (Figure 4A), later revealed stooling via the anus. Purse-string suture stoma closure at the eleventh

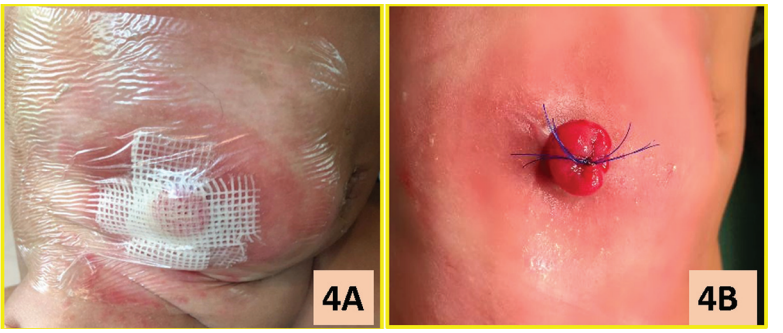

Figure 4. Trial period of temporary ileostomy closure with occlusive dressings at home (A). Purse string suture closure was later secured at the age of 11 months (B).

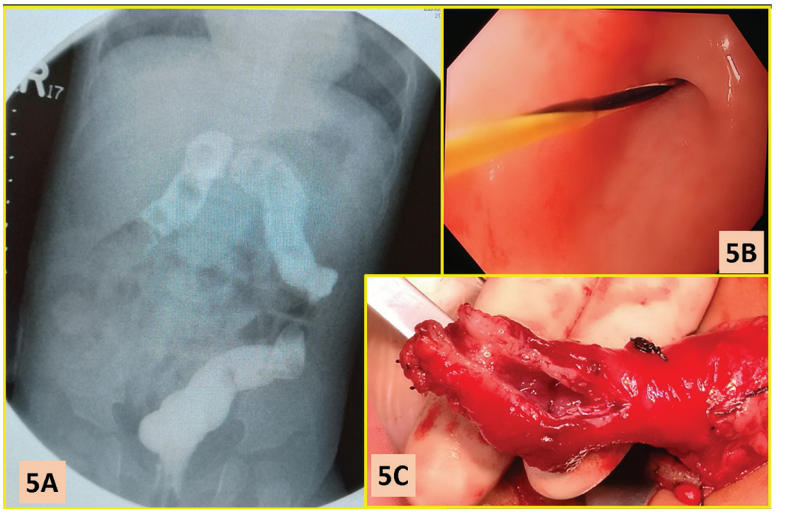

Figure 5. A 3rd contrast enema study demonstrating a narrowed segment of descending colon near splenic flexure which had never been subject to biopsy (A). Colonoscopy exam showed a narrowed lumen that a guidewire could pass through and a balloon catheter could not dilate (B). Intra-operation finding of a 3-cm narrowed fibrotic stricture colon (C).

month of life (Figure 4B) was then scheduled. With bowel effluent content witnessed dribbling from the closed ileostomy, a third contrast enema study revealed a narrowed region within the descending colon near the splenic flexure, which was never a biopsy site, raising a differential working diagnosis of precedent medical NEC (Figure 5A). Colonoscopy showed a narrowed bowel lumen that a guidewire would pass through, however a balloon catheter could not successfully dilate the stricture (Figure 5B) at which time laparotomy revealed a 3-cm fibrotic colonic segment (Figure 5C). At the time of stricture resection re-biopsies were then taken that later confirmed ganglion cells in the descending colon and rectum. Following colon stricture resection regularly stooling occurred from the anus indicating functional recovering of colonic motility with closure of the Santulli enterostomy. At the last clinic office visit follow-up, at four years of age, the patient had steadily recovered with body-weight-gain and a normal stooling pattern comparable to her healthy twin sister.

In conclusion, the present index case report highlighted that the infant's colon later functioned well with a normal stooling pattern with pathology exam showing mature ganglion cells at eleven months (Table 1).

Narrative Review

Pathophysiology

The pathoembryology of HD is widely applicable to all HD-variants[10]. Studies on some 100 babies through detailed reporting examination show that immature ganglion cells may be present until two years of age raising the possibility of a developmentally regulated physiological process[7]

Table 1. Timetable - patient illness course

Age	Events
10 days	Trans-umbilical vein and artery catheterization
3 months	1st plain abdominal film X-ray confirms gross intestinal dilatation and a non-diagnostic contrast enema study
4 months	Equivocal levelling intestinal biopsies/loop ileostomy
6 months	Prolapsed loop ileostomy
7 months	Santulli ileostomy/2nd gut biopsies reveal mixed mature ganglia cells
9 months	Bowel training adaptive program/temporary occlusive dressing applied to the stomal site
11 months	Purse-string ileostomy closure/contrast study later showed a colon stricture/3rd gut biopsies reveal mature ganglia cells
15 months	Permanent ileostomy closure/full recovery achieved with normal stooling

further supported with growing evidence that refers to acquired maturation of ganglia cells occurring over time notably after the age of three months[2,3,6,11-13]. Mixed mature and immature ganglion cells in the same gut region, as in the present case may be readily explained by (i) two different sites of origin, vagal and sacral neural crest cells[9], (ii) two different migratory fate routes, neural crest cells cross the mesentery and/or along the intestine(9), (iii) ganglion cells in the myenteric plexus mature earlier than submucosal plexus[2], and (iv) area(s) of variable defined transitional zone sites[9]. Ola et al. further speculated that the pathogenesis of immature ganglia cells may be also associated with delayed maturation and late cell death[14].

Clinical presentation and diagnosis

The clinical manifestations of index patients with IMC are typically observed on the first day of life[3], similar to those of HD particularly TCA[12] as a functional lower gastrointestinal obstructive illness with abdominal distension, delayed passage of meconium[3,6,11,12] with irregular stooling pattern[2,3]. The working differential diagnoses well describe allied disorders notably meconium ileus and meconium plug syndrome[15]. A recent systematic review and meta-analysis has revealed HD in 5% to 6% of preterm infants, a much rarer frequency occurrence than that recorded in term newborns[1]. From these data, premature infants may show a transient impairment of gut peristalsis with functional bowel obstruction resultant from immature ganglia[1,2,6] rather than HD particularly with the hallmark findings of poor identification of hypertrophic nerve fibers[2,8]. Currently a confirmatory diagnosis from histopathology mandates reports 'immaturity of colonic ganglia cells'[5]. Indeterminate diagnosis from histology examination will require further detailed investigations including anorectal manometry as a screening tool exam testing the recto-sphincteric reflex in infants typically aged more than 6-months[16,17], and/or contrast transit time marker bead studies[18].

Investigations

1. Contrast enema

Contrast enema is a common investigation for intestinal motility disorders that may show typical features of IMC including microcolon and/or residual contrast retention[11,12,17,19]. No solid studies currently exist on the precise accuracy or concordant rate(s) of establishing a firm diagnosis between contrast enema and histopathology in IMC while good agreement exists in HD[20], which has a 50% accuracy[21] and an 88% concordant rate in accurate identification of the transitional zone[22].

2. Histopathology

The gold standard test for firm diagnosis of IMC depends on accurate histopathology study[2,8,23,24]. The hallmark features of immature ganglia cells are their small size, dark nuclei, small nucleoli surrounded with basophilic cytoplasm[2,3,24] that may be easily misinterpreted as lymphocytes and endothelial cells[2,3,6] and may create a challenging histological dilemma for pathologists particularly in the setting of suboptimal biopsy specimens[7-9]. These findings may distinguish HD and IMC if the pathologist(s) did not accurately specify reporting visualizing hypertrophic nerve fibers leading to the erroneous diagnosis of HD in case(s) of IMC and vice versa[8,9]. In these indeterminant clinical scenarios, pediatric surgeons may be compelled to perform an unnecessary resection pull through operation to effect curative therapy(s) in IMC under the erroneous patient misdiagnosis of HD.

Special stains facilitate the ready identification of immature ganglion cells such as nicotinamide adenine dinucleotide phosphate diaphorase (NADPHd), neural cell adhesion molecule (NCAM) staining, and succinate and lactate dehydrogenase (SDH &

LDH)[2,3]. The palisading-like arrangement(s) of ganglion cells, the linear arrangement patterning along the border of myenteric plexus, will also improve the diagnostic yield accuracy of immature ganglia[24].

3. New technologies for HD may be adapted for IMC

Intraoperative confocal laser endomicroscopy can identify wavy linear structures produced by hypertrophic nerves and ladder-like structures of the enteric plexuses for HD-diagnosis. Intricate question(s) on how these different new findings feature and demonstrate the various stages of intestinal ganglia cell maturation are insightful[25].

Treatment

With reference to recent literature published since 2023 no clear consensus exists on the best management of IMC[4,6] even if studies or narrative reviews on HD have been growing exponentially[1,5,8,10,16,26-30]. Indications for surgery in IMC are thus highly controversial. Some patients reportedly are doing well after stoma closure and others following a resectional pull-through operation as for HD[6,11,12]. Optimal timing for expectant therapy in symptomatic babies is uncertain[6,11] with little, if any, reference recommendation(s) that exist on the timing of gut re-biopsy[3]. It should be further noted that the presence or existence of mature ganglia cells on histology does not always correlate with intestinal recovery or clinical symptomatic improvement[6,11].

Expectant management

Treatment plans may therefore rely on promoting or aiding mechanisms of defecation(s) notably use of intestinal prokinetic agents[3], stool softeners[3], laxatives[2,3,12], glycerin suppository(s)[6], enemas[2,3,11], cholinesterase inhibitors or neostigmine[3], daily bowel flush irrigations[18], and bi-directional gastrointestinal decompression using gastric and anal tubes[3]. These therapy options are however strictly more applicable to term babies[12].

Diverting enterostomy

Undertaking a primary resectional pull-through operation for a patient suspected of having HD or its phenotype variants[30] may erroneously lead IMC patients with unrecognized immature ganglia cells, to lose their potentially normal native functioning rectum. Diverting enterostomy in uncertain cases is thus preferable to allow a period of oral feeding particularly in preterm babies[12,18] while awaiting full histopathological reporting[3,30], and then decision making on next best options[22]. From accumulated knowledge of the benefits of bowel diversion the T-type Santulli enterostomy has been deployed for varied infantile gastrointestinal diseases[11,31] and double-barreled and loop enterostomies have also been used in patients with suspected HD[4,6,11,12]. As shown in this illustrative infant case report, a Santulli enterostomy proved extremely valuable, facile, and adaptable in the IMC patient[11].

Prognosis

IMC patients are considered to have a favorable prognosis[24] and may achieve a successful outcome with efforts tailored at conservative management without enterostomy[3,12]. Reports show normalization and maturation of ganglia with intestinal motility acquired usually before one year of age[3,11,12,24].

Discussion

HD is a classical working diagnosis for a newborn with delayed passage of meconium and abdominal distension with full histological confirmation of disease that will show absence of ganglion cells on rectal biopsy. In this IMC case study, surgical management was emergently undertaken with levelling biopsies and creation of a double enterostomy due to (i) recurrent abdominal distension and poor response to rectal irrigations, (ii) coexistent malnutrition with failure to thrive, and (iii) atypical contrast enema findings for HD. With a lack of positive and definitive histopathological confirmation of disease, regular clinical monitoring of stooling patterns was a useful strategy plan for the patient. With basic knowledge and understanding that intestinal ganglion cells maturation coordinates with improved intestinal motility functional recovery can be expected to evolve with age[6,11]. The Santulli enterostomy crucially allowed clinical care to progress for this patient that later permitted a full functional recovery.

Although there was no firm early diagnosis of NEC, the history of previous umbilical catheterization, neonatal sepsis, and the occurrence of a late stricture at the watershed area of the colon raised a distinct possibility of unrecognized NEC co-related to IMC[17].

Conclusion

Newborns with an atypical clinical history who have a non-classical contrast enema study report should be considered as having a rare variant bowel

innervation disorder such as IMC. The present case highlights a care plan strategy that successfully allowed bowel maturation and functional recovery to occur thus crucially allowing the patient to avoid having a resectional pull through operation as for HD.

What is already known about this topic?

IMC may often be encountered in premature newborns until intestinal maturation is achieved. It is essential that pathology examination accurately distinguishes immature ganglionic cells from other similar featured cells. Timing and scheduling for repeat biopsy in infancy remains poorly defined.

What does this study add?

Bowel training aided by a Santulli stoma may allow babies to develop functional intestinal maturation with re-biopsy helping guide definite management and recovery. Crucially in this illustrative case report, normal stooling was achieved after stoma closure thus avoiding a resectional pull through operation as for HD. Expert pathology services are essential to guide best surgical practice.

Ethics approval and consent to participate

Ethics Committee Faculty of Medicine Ramathibodi Hospital, Mahidol University granted and approved the case presentation (No. MURA2022/103).

The informed consent for using all patient's data and related images or photographs was obtained from the patient's legal guardian (mother).

Conflicts of interest

The authors declare no conflict of interest.

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