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Total Intestinal Aganglionosis- A Deadly Masquerader!

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Abstract

Background: *Total Intestinal Aganglionosis is an extremely rare variant of Hirschsprung's disease (HD). Studies based on this malady are limited in literature, due to its rarity and its ability to masquerade as other surgical pathologies, thereby delaying and often preventing its correct diagnosis. This is a case series that describes its three varied presentations and subsequent management of it.*

Method: *Retrospective observational study in a tertiary care centre in India. Clinical and operative data was retrospectively assessed from records from 2016 till 2023.*

Results: *All three cases caused initial diagnostic dilemma- First case was diagnosed as meconium ileus and underwent Bishop Koop ileostomy. Second case was diagnosed as type I jejunal atresia and underwent resection anastomosis. Third case was suspected to be small bowel HD and underwent leveling jejunostomy. Multiple laparotomies were needed for all three cases, as there was no clinical improvement with first laparotomy. Histopathology proved to be crucial in clinching the final diagnosis of total intestinal aganglionosis. Ziegler's myotomies were found to be effective for the first case, albeit for a brief period.*

Conclusion: *Total Intestinal Aganglionosis is a rare entity that can masquerade as other surgical conditions in neonates leading to delayed or missed diagnosis. Routine biopsy can be taken in suspicious cases to rule out this ominous pathology. Autologous intestinal reconstructive procedures along with intestinal rehabilitation may become the ideal solution to this deadly masquerader, in the long run.*

Keywords: *total intestinal aganglionosis, Hirschsprung's disease, Ziegler's myotomy, autologous intestinal reconstruction, total parenteral nutrition.*

Background

Despite advances in surgical and medical management of Hirschsprung disease and Short bowel syndrome, the management of Extended total colonic aganglionosis (ETCA) variant remains challenging and is associated with poor outcomes and high mortality rates up to 36%–80%[(1)]. Literature is scanty on this topic due to its rarity. It can go undiagnosed as it can masquerade other surgical pathologies. This case series aims to shed some light on its varied presentations, diagnosis and subsequent treatment options.

Method

Aim of this study was to describe the varied presentations of total intestinal aganglionosis, diagnosis, disease course, treatment and subsequent complications. This was a retrospective observational study, conducted in a tertiary care centre in Kerala, India. Clinical and operative data of all cases with histopathologically proven TIA/NTIA were retrospectively assessed from records for a duration of eight years, from 2016 till 2023.

Case 1

The first case was a term, female baby who presented with abdominal distension and bilious vomiting soon after birth. Initial workup (plain X-ray abdomen (fig.1a), contrast enema study (fig.1b)) was suggestive of meconium ileus. Bishop Koop ileostomy was done. Regular stoma washes were given through it. She was supported with total parenteral nutrition (TPN). However, the bowel did not open up and intestinal obstructed persisted. Child underwent relaparotomy. No definite cause for obstruction was found on gross inspection. Hence conversion to divided ileostomy along with multiple seromuscular biopsies (to rule out any underlying aganglionosis) was done. All biopsy specimens including proximal small bowel was aganglionic. As there was no improvement in the child's condition, a third laparotomy along with multiple Ziegler's myotomies (5cm long incisions upto submucosa along antimesenteric border, followed by spreading of the cut surface to a width of 1cm) till stoma site, were done. Stoma started functioning for a brief period and trophic feeds were started. However, the child succumbed to sepsis two months after birth.

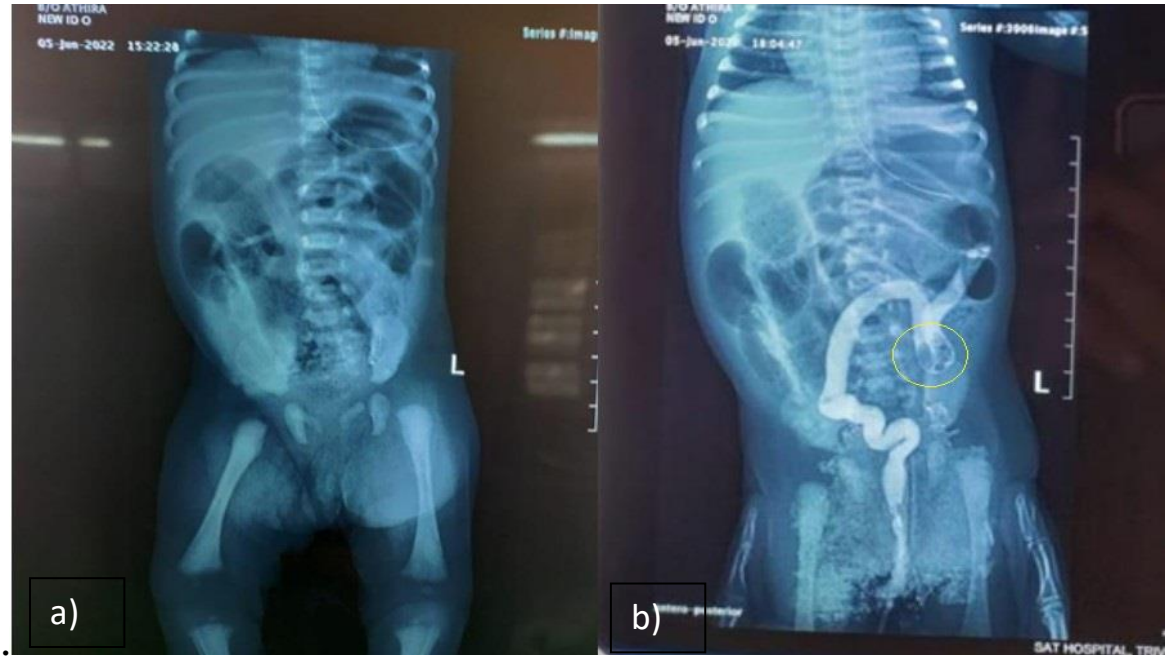

Figure 1a) Ground glass appearance of bowel without any air fluid interfaces, noted in plain X-ray abdomen. **b)** Microcolon with meconium pellets in contrast enema

Case 2

Second case was an extremely preterm, female baby. Antenatal ultrasounds were suggestive intestinal atresia. Postnatal, child presented with abdominal distension along with bilious aspirate (fig.4). Plain X ray abdomen (fig.2a) and upper GI series (fig.2c, 2d) was suggestive of partial proximal bowel obstruction and type I proximal bowel atresia was suspected. On laparotomy, jejunum was found to be dilated, 15cm from duodeno-jejunal (DJ) flexure along with an intraluminal web (fig.2b). Jejunal web resection with end to end anastomosis was done. The anastomosis failed to function and bilious aspirate persisted. Meanwhile, she was supported with total parenteral nutrition. A second laparotomy was done on postoperative day 14. There was a thickened area proximal to the anastomosis. Redo anastomosis (suspecting anastomotic stricture) along with multiple seromuscular biopsies were done. All biopsies came as aganglionic. Postoperatively, child developed anastomotic leakage. A third laparotomy along with redo anastomosis (as parents were not willing for stoma) and multiple myotomies were done. However, the child did not survive and expired after 1 week.

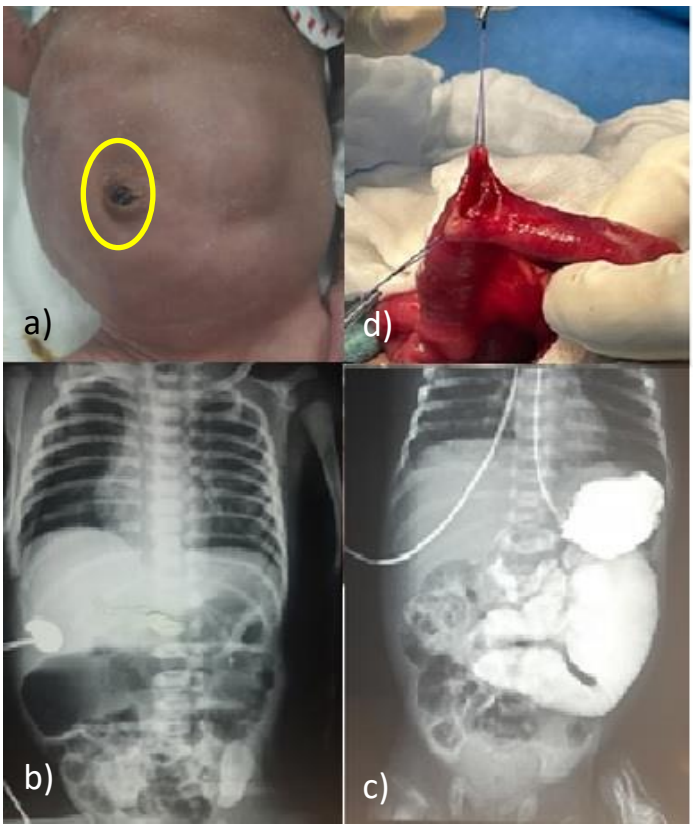

Figure 2a) Dilated visible loops seen on abdomen**. b)** Plain X-ray abdomen showing dilated proximal bowel loop**. c)** Contrast study showing distended proximal bowel loop. **d)** Intraluminal web found at the transition zone.

Case 3

The third case was a term, male baby who presented with abdominal distension and bilious vomiting on post natal day 2. Abdomen X ray was suggestive of intestinal obstruction and child was taken up for surgery. On laparotomy, a transition zone was noticed at mid jejunum, 20cm from DJ flexure. (fig.3). Suspecting small bowel HD, leveling jejunostomy along with multiple seromuscular biopsies were done. However, postoperatively child showed no improvement, stoma did not function and bilious aspirate

persisted. Histopathology showed absence of ganglion cells in all specimens including stoma site. Meanwhile the child was supported with total parenteral nutrition. On second laparotomy, stoma revision to proximal jejunum, 5cm from duodeno-jejunal (DJ) flexure was done. Still, the stoma failed to function. Child went into septic shock and could not be revived. He expired one month after birth.

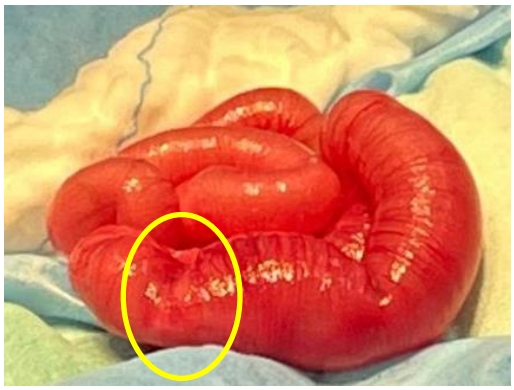

Figure 3- transition zone noted 20cm from DJ flexure (yellow circle)

Results

In this case series, all the three patients had presented in the newborn period. They did not have any definite signs or features suggesting a diagnosis of NTIA/TIA initially. First case was initially diagnosed as meconium ileus and underwent Bishop Koop ileostomy. Second case was diagnosed as type I jejunal atresia and underwent resection anastomosis for the same. Third case was suspected to be small bowel HD and underwent leveling jejunostomy. (Table 1)

Common features for all three cases were

1. Presentation within 48 hours after birth with features of bowel obstruction
2. Initial laparotomy did not reveal the definitive pathology.
3. Clinical condition did not improve following initial procedures(which pointed to an alternate diagnosis)
4. Multiple laparotomies were needed along the disease course.

There was no history of similar illness in family. The male: female ratio was 1:2.

X-ray findings duly noted in these cases include,

1. Dilated small bowel loops.
2. Ground glass appearance of bowel without any air fluid interface(case 1)
3. Microcolon with meconium pellets in contrast enema (case 1)
4. Multiple air fluid levels (case 3)

Histopathology proved to be crucial in clinching the final diagnosis. Conventional Haematoxylin and Eosin staining (fig 4) and special staining with calretinin were used, on all specimens. Findings noted include

1. Absence of ganglion cells in Meissner's and Auerbach's plexus
2. Hypertrophic nerve bundles seen.

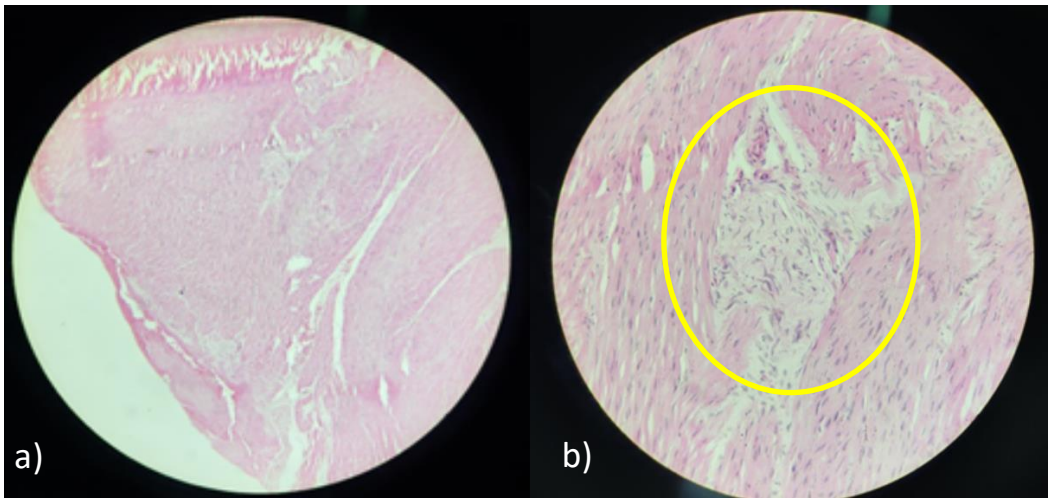

Figure 4.a) Haematoxylin and Eosin stained seromuscular biopsy specimen demonstrating the absence of ganglion cells in intermuscular zone. **b)** Magnified view showing hypertrophied nerve trunk(yellow circle)

Here the level of aganglionosis extended proximally atleast upto DJ flexure in all three cases, with the most proximal biopsy taken from stomach (third case). Partial thickness extramucosal biopsies (0.5cm x 0.5cm) along with full thickness doughnut biopsies at the level of stoma were taken to determine the level of aganglionosis.

Ziegler's myotomies were found to be effective in the first case. There was some improvement and oral feeds were started. However, the child ultimately succumbed to sepsis.

All three patients in this case series died within 2 months after birth. None of the cases underwent gastrostomy, which may have helped in decreasing aspiration risk, if they had survived. Children with TIA are at high risk for sepsis and death. Probable causes include-

1. Dependence on parenteral nutrition and central line access
2. Frequent enteritis and bacterial translocation
3. Multiple interventions including laparotomies increases their chance of catching an infection with resistant organisms
4. Prolonged nil per oral status may be needed.
5. Immunological immaturity during the newborn period.
6. Liver failure due to prolonged parenteral nutrition.

Table 1- Summary of the three cases with NTIA/TIA

Case no	Pre-op diagnosis	Procedures	HPE	Outcome
1.	Meconium ileus	Bishop Koop ileostomy → divided ileostomy+ multiple biopsies → Ziegler's myotomies + biopsies	Absent ganglion cells	Fatal
2.	Jejunal atresia	Resection anastomosis → redo anastomosis + multiple biopsies → redo anastomosis	Absent ganglion cells	Fatal
3.	Small bowel HD	Leveling jejunostomy → stoma revision to proximal jejunum	Absent ganglion cells	Fatal

Discussion

Patients with NTIA/TIA will usually have 10–130 cm of normally innervated proximal small bowel and will present shortly after birth with intestinal obstruction. Confirmation of the aganglionosis extent will usually require several interventions as the diagnosis may be missed initially. Ideally, the first exploration should include multiple large and small bowel biopsies and creation of an ostomy at the most distal loop that appears normally innervated. Children with NTIA/TIA require gastrostomy and central venous access for parenteral nutrition, and are best managed by a multidisciplinary intestinal rehabilitation programme[(2)]

Survival of NTIA/TIA patients have improved due to parenteral nutrition (PN), which enabled maintaining a satisfactory nutritional state. However, long-term treatment with PN increases susceptibility to sepsis and end-stage liver disease.

Since the late 1980s, several surgical techniques have been developed to enhance residual intestinal function considered as autologous intestinal reconstructive procedures (AIR). Among these techniques are Ziegler's myectomy-myotomy, Kimura's procedure, Bianchi's lengthening procedure and serial transverse enteroplasty (STEP)[3] AIR surgery is an useful and effective way to enhance residual bowel absorptive function and to reduce parenteral nutrition requirements. The more proximal site (30 to 35 cm below the ligament of Treitz) of jejunostomy with myectomy-myotomy modification is recommended for prolonged survival[4]

Ziegler's myectomy-myotomy was originally described as extending an antimesenteric myectomy-myotomy from the ganglionic-aganglionic transition zone for variable lengths, the operative design being to create sufficient small bowel length to support life. From the transition zone to 10 cm distally, a myectomy was done removing a 1 cm wide length of seromuscular tissue to the level of the submucosa. From the distal end of the myectomy, another 40 cm of bowel received an antimesenteric border myotomy upto the submucosal level followed by spreading of the cut surface to a width of 1 cm. The myectomized bowel was terminated as an end-stroma or as an isolated jejuno-ileal segment[4] Various mechanisms contributing to the effectiveness of this procedure includes

1. extended myectomy-myotomy relieves the obstruction of NTIA/TIA
2. aganglionic bowel after extended myectomy-myotomy acts as a passive conduit for proximally propulsed nutrients; and
3. aganglionic bowel after extended myectomy-myotomy undergoes adaptive change and is capable of absorbing life-supporting nutrients.

In 2003 a conceptually simple bowel lengthening and tapering operation called the serial transverse enteroplasty operation (STEP) was introduced. A contraindication to surgery is end-stage IFALD with portal hypertension; in this case transplantation rather than STEP is recommended. The STEP procedure is based on the alternate transverse application of surgical stapling devices to dilated proximal ganglionated bowel using a transmesenteric approach. A zigzag lengthening and tapering of the intestine ensues.

The salient advantages of this operation are that it is technically straightforward, can form a uniform bowel channel regardless of variable underlying proximal bowel dilation, and can be repeated if the bowel subsequently redilates. PN-dependent children who have been treated with the STEP operations have shown statistically significant increases in weight for age Z score, weight for height, upper arm anthropomorphic tests, D-xylose absorption, and enteral tolerance.[3]

Other promising approaches to AIRS are bowel stretch and the tissue engineering of small intestine. Using tissue-engineering principles, neonatal rat intestine has been implanted on a scaffold and anastomosed to the remaining bowel. Further, the implantation of VEGF microspheres into the construct appeared to increase epithelial proliferation and microcapillary density.[3]

Intestinal or combined intestinal-liver transplantation are also optional treatments in patients who develop irreversible intestinal failure with or without liver failure. Nevertheless, after initial enthusiasm for transplantation as possible definitive treatment for patients with NTIA/TIA, most recent data reported limited grafts' and patients' survival related to destructive alloimmunity and immunosuppressive treatment side effects. Consequently, after being perceived as nutritionally non-beneficial and largely abandoned, AIR techniques are regaining their place in the surgical management of TIA/NTIA patients.

Preserving an aganglionic bowel segment, combined with a customised surgical approach and dedicated intestinal rehabilitation programme, proves effective in minimising morbidity and mortality rates. A large-scale multicentre study should compare short- and long-term outcomes of

this treatment approach with those of intestinal transplantation to dictate guidelines.

Conclusion

Total Intestinal Aganglionosis is a rare entity which can masquerade as other surgical conditions in the neonate leading to delayed or missed diagnosis. In this case series, all three babies presented within 48 hours after birth with features of intestinal obstruction. Initial diagnostic dilemma was solved with the help of histopathology. Routine biopsy can be taken in suspicious cases to rule out this ominous pathology. Autologous intestinal reconstructive procedures along with intestinal rehabilitation may become the ideal solution to this deadly masquerader, in the long run.

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