

Atypical onset of total colonic Hirschsprung disease in a small female infant

A case report

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Abstract

Rationale: Hirschsprung disease (HD) or colonic aganglionosis is a congenital disorder, which results from the abnormal migration of neuronal cells of the neural crest leading to a disorder of the enteric nervous system consisting in the absence of ganglion cells within the submucosal and myenteric plexus.

Patient concerns: We report the case of a 7-month-old female infant admitted in our clinic for constipation and failure to thrive. At the age of 6 months, she was examined in our clinic for the same reasons, and we recommended symptomatic treatment without improvements. The clinical examination revealed pallor of the skin and mucosa, distended abdomen, and abdominal tenderness at palpation.

Diagnoses: The abdominal ultrasound showed abdominal bloating, and the barium enema was normal. The patient's evolution worsened progressively within the following 3 days after admission associating signs of toxic megacolon.

Interventions: She underwent a surgical intervention with total colectomy and ileostomy, and the final diagnosis confirmed by the histological examination was of total colonic aganglionosis (TCA).

Outcomes: The evolution immediately after the surgery and the follow-up examination after approximately 3 months pointed out normal weight gain and the laboratory tests were within normal limits.

Lessons: TCA can also manifest in older infants. Barium enemas can guide the diagnosis in most cases of HD. Nevertheless, in patients with TCA, it can be normal. Moreover, it could represent a trigger for toxic megacolon.

Abbreviations: AST = aspartate aminotransferase, Hb = hemoglobin, HD = Hirschsprung disease, TCA = total colonic aganglionosis.

Keywords: Hirschsprung disease, infant, total aganglionosis

1. Introduction

Hirschsprung disease (HD) was first reported in 1886 at the Society of Pediatrics in Berlin, by Harald Hirschsprung, a Danish pediatrician.^[1] HD or colonic aganglionosis is a congenital disorder, which results from the abnormal migration of neuronal

cells of the neural crest leading to a disorder of the enteric nervous system consisting in the absence of ganglion cells within the submucosal and myenteric plexus.^[2–4] This condition has an incidence of 1 in 5000 live births and it occurs more frequently in men, with a male-to-female ratio of 4:1.^[2] According to the length of the aganglionic colon, HD can be divided into 3 groups: short-segment, long-segment, and total colonic aganglionosis (TCA).^[5] TCA is the rarest form of all occurring in approximately 1:50,000 live births, accounting for approximately 5% of all cases,^[3,6] while up to 75% of the cases present with rectosigmoid impairment.^[7] TCA also affects predominantly men, but with a smaller ratio, of 2:1.^[6] The incidence of HD varies depending of ethnicity. Therefore, the incidence per 100,000 live births in Caucasians, Africans, and Asians was reported as it follows: 15, 21, and 28, respectively.^[8] Most of the cases of HD are sporadic, but genetic studies underlined the contribution of over 10 genes in its pathogenesis, including RET, GDNF, EDNRB, EDN3, and others.^[9] Nevertheless, these mutations account only for approximately one-half of all cases of HD.^[9] Also, dominant and recessive patterns of transmission were identified in family groups.^[3] Other genes, such as LICAM, SOX10 and ZFH1B, were associated with syndromic forms of HD.^[3]

HD usually manifests within the first days after birth by a distended abdomen, the inability to eliminate meconium, and/or bilious emesis expressing feeding intolerance.^[3] Other reported symptoms consist in failure to thrive with hypoproteinemia,

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enterocolitis, encopresis, with an empty rectum at examination.^[3] Therefore, clinical manifestations are essential in guiding the diagnosis, but further investigations are required in order to establish the diagnosis. Therefore, contrast enema and anorectal manometry can be of real help in patients suspected with HD, but the latter one can be difficult in infants.^[3] Barium enema is very useful in assessing the extent of the aganglionic segment, and it will probably help the diagnosis in children above the age of 1 month due to the fact that the normal segment of the bowel needs a certain amount of time to dilate.^[3] However, up to 10% of infants with HD present no changes on contrast enemas requiring 24-hour delayed films that will show retained contrast. Therefore, the presence of a significance amount of barium within the bowel after 24 hours increases the suspicion of HD even in the absence of other suggestive signs.^[3] Nonetheless, the histological examination remains the gold standard of the diagnosis, which will confirm the lack of the ganglions at the level of the submucosal plexus along with neural hyperplasia on rectal suction biopsy specimens or full-thickness ones from the rectal posterior wall 2 cm above the dentate line in order to eliminate false-positive results.^[4]

The treatment of HD is surgical and it consists in the resection of the aganglionic colon followed by a temporary ostomy followed by surgical reconstruction with the suppression of the ostomy when the child reaches 8 to 12 months of life. However, it seems that many patients who undergo surgical repair experience bowel disorders many years after the treatment.^[10] Enterocolitis along with toxic megacolon are the most severe life-threatening complications of HD that can occur before and after the surgical intervention.^[11]

The aim of this case report is to underline the atypical onset of total colonic HD regarding both clinical manifestations and age in a small female infant.

The informed consent was obtained from the patient's mother prior to the publication of this case report.

2. Case report

2.1. Presenting concerns

We report the case of a 7-month-old female infant admitted in our clinic for constipation and failure to thrive. Her personal history revealed the fact that at the age of 6 months she was examined in our clinic for the same reasons, and we recommended treatment with lactulose and probiotics, but without any improvement. We mention that the infant was fed exclusively with milk formula since birth because according to the mother, the neonatologist diagnosed her with lactose intolerance. No other perinatal pathological events were identified.

2.2. Clinical findings

The clinical examination at the time of admission revealed the following pathological elements: pallor of the skin and mucosae, distended abdomen, painful at superficial, and deep palpation. The infant weighed 5.7 kg at the time of admission.

2.3. Diagnostic focus and assessment

The initial laboratory tests pointed out hypochromic microcytic anemia (hemoglobin [Hb] 10.2 g/dL, hematocrit 31.5%, medium erythrocyte volume 70.2 fL, medium erythrocyte hemoglobin 22.7 pg), and a mildly increased aspartate aminotransferase (AST 33.9 U/L). The abdominal ultrasound showed severe abdominal

bloating. We performed a barium enema that did not reveal any obvious dilations or stenosis, with a normal colonic motility, suggesting only a functional constipation. Unfortunately, the day after this contrast investigation the infant's status begun to deteriorate associating feeding refusal, severely distended abdomen, abdominal tenderness, and influenced general status. We inserted a rectal catheter for gas in order to decrease the abdominal bloating, but without any obvious results. After another day she developed fever with the lack of transit for feces. Therefore, we repeated the laboratory test, which revealed severe leukocytosis (30,400/ μ L), hyponatremia (Na 129.9 mmol/L), hypopotassemia (K 3.7 mmol/L), increased inflammatory biomarkers (C-reactive protein 100 mg/L, erythrocyte sedimentation rate 50 mm/h), and elevated AST (35 U/L). We also repeated the abdominal, which pointed out dilated intestinal loops. We raised the suspicion of toxic megacolon and we referred the patient to a pediatric surgeon who decided to perform a surgical intervention identifying severe dilation of the entire colon, and the histological examination pointed out TCA.

2.4. Therapeutic focus and assessment

The patient benefited by total colectomy with ileostomy. The postsurgical evolution was favorable, and the patient was discharged after approximately 2 weeks.

2.5. Follow-up and outcome

The follow-up examination after 3 months from the surgery pointed our favorable evolution, a normal weight gain, and the laboratory tests were within normal ranges. Most-likely, after the age of 1 year, the patient will benefit from ileostomy suppression and a surgical repair of the bowel if the evolution remains favorable.

3. Discussion

TCA is the rarest form of HD accounting for up to 5% of all HD cases.^[3] Most infants with this form are diagnosed within the first 10 days after birth.^[12] Similarly, a review performed on 91 Irish patients underlined that 99% of patients presenting total colonic HD are diagnosed before the age of 3 months.^[13] Also, it seems that total colonic HD affects predominantly males.^[6] Contrariwise, our case describes a diagnosis of TCA in a 7-month-old female infant. Similarly, Short et al recently described a case of a 9-month-old female infant who presented with small-bowel obstruction associating right-sided colonic diverticula, who was eventually diagnosed with TCA.^[14] TCA was reported to be associated with colonic diverticulosis also by other authors in the past in both infants^[15] and even more important in a 37-year-old man.^[16] The latter case underlines the extreme possibility of delay in diagnosing TCA.^[16] Nevertheless, in our case, we did not identify any colonic diverticula. Contrast enemas are usually useful for diagnosis HD. Findings on barium enema that may suggest total colonic HD are diminished colonic haustra, a question mark-shape colon, a smaller colon regarding both the length and the caliber, but studies also showed that this investigation cannot be reliable for diagnosing TCA in certain cases.^[14,17] Similarly, in our case, the barium enema did not reveal any pathological signs suggestive for HD. Likewise, the case mentioned above, reported by Short et al, also did not present any transition zone or other signs on contrast enema that would raise the suspicion of HD.^[14] Moreover, a case series study

performed on 25 patients from a single institution that were diagnosed with TCA underlined that radiographic studies present a diagnostic rate of <30% in this group of patients.^[18] Therefore, the histological examination of rectal biopsies and colonic biopsies remains the gold standard for the diagnosis of HD. Even though immunohistochemistry techniques are widely used for the diagnosis of HD in developed countries, hematoxylin–eosin staining presents a moderate reliability for this diagnosis, but it can be used in case of the lack of more expensive immunohistochemistry techniques.^[19] A recent study underlined that the histological examination of the appendix is a very useful tool in the diagnosis of TCA.^[13]

Even though the etiology of HD remains unknown, genetic susceptibility is well-documented to have an important role in its development. Thus, HD has been reported to be associated with other genetic conditions, such as Down syndrome, or other anomalies, like cardiovascular, gastrointestinal, or urogenital one.^[3,7,20] Nonetheless, in our patient, we did not find any other associated syndromes or anomalies. The clinical signs of HD present a wide individual variability, but the patients usually present with long-term constipation and distended abdomen, or, in case of children, failure to thrive with hypoproteinemia.^[3] Nevertheless, functional constipation must also be taken into account into the differential diagnosis as the most frequent cause of constipation with negative psychosocial impact.^[21] Also, in rare cases constipation can be caused by celiac disease,^[22,23] it can be associated with giant colonic polyps leading to subocclusive symptoms,^[24] or with nutritional disorders, such as obesity in children.^[25] Our patient also presented with constipation and failure to thrive, but she did not associate hypoproteinemia. HD can also lead to complications, especially in patients with delay in the diagnosis and treatment. HD-associated enterocolitis is the most severe complication of this condition that can lead in extreme cases to toxic megacolon.^[11] Toxic megacolon is defined by total or segmental colonic dilation along with systemic toxicity,^[26] and it can appear also associated with inflammatory bowel diseases.^[27] This severe condition can be the first manifestation in previously undiagnosed HD patients, and it usually carries high mortality rates.^[26] Our patients also presented initial signs of toxic megacolon, such as fever, severely dilated colon, leukocytosis, and elevated inflammatory biomarkers, but fortunately the surgical intervention was performed soon enough in order to avoid a fatal outcome. The same authors underlined that in cases of toxic megacolon associated with HD, the medical treatment presents no benefits, and due to the high mortality rate of this condition, the patients should undergo a surgical resection of the massively distended colon even with ileostomy if needed in order to improve the survival rate.^[26] Therefore, the treatment of TCA consists in total colectomy with a bridging ileostomy followed by a surgical repair as a secondary intervention.

The outcome of patients diagnosed with TCA is burdened by multiple bothering events, such as obstructive symptoms, parenteral nutrition, or even a permanent stoma. Therefore, it is advisable to state that patients with TCA need lifelong monitoring of multidisciplinary teams due to its negative impact on patients' social life in order to increase as much as possible their life quality.^[28,29]

4. Conclusion

The form of HD consisting in TCA is a rare condition that is usually diagnosed within the first days after birth. Nevertheless,

this form can also manifest in older infants. Even though HD affects predominantly males, our case described a female infant. Barium enemas can guide the diagnosis in most cases of HD, but in patients with total aganglionosis can be normal and could represent a trigger for toxic megacolon.

Author contributions

Cristina Oana Mărginean, Lorena Elena Meliț, and Cristian Dan Mărginean conceptualized and designed the study, drafted the initial manuscript, and revised the manuscript. Horea Gozar performed the surgical procedure, collected data, and revised the manuscript. Eموke Horvath performed the histopathological analysis of the samples. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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