Journal of Pediatric Surgery 56 (2021) 454–458

Contents lists available at ScienceDirect

Journal of Pediatric Surgery

journal homepage: www.elsevier.com/locate/jpedsurg

Immune function and infectious complications in children with jejunoileal atresia☆

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ARTICLE INFO

Article history:
Received 17 March 2020
Received in revised form 19 May 2020
Accepted 24 May 2020

Key words:
Children
Intestinal atresia
Jejunoileal atresia
Multiple intestinal atresia
Immunodeficiency

ABSTRACT

Objective: Little is known about differences in immune function among children with multiple intestinal atresia (MIA) and those with isolated intestinal atresia (IA), and how such differences may manifest as infectious complications and patient outcomes. This study aimed to investigate the immune function and its impact on patient outcomes in IA and MIA children.
Methods: A single-center retrospective cohort study included children aged 0–19 years with intestinal atresia who were referred to a multidisciplinary intestinal rehabilitation program from 1/2000 to 12/2016. Data were collected for patient characteristics, surgical history, immunologic work-up, and infection-related hospitalizations. Groups of IA and MIA children were compared using chi-square test or Fisher's exact test for categorical variables and using Mann–Whitney test for continuous variables, as appropriate.
Results: Twenty-seven children (18 IA, 9 MIA) were included. More than half of the patients had low CD counts for age in IA and MIA groups: CD3 58.3% vs. 66.7% ($p = 1.0$), CD4 50.0% vs. 66.7% ($p = 0.7$), CD8 67.7% vs. 88.9% ($p = 0.3$), respectively. Six out of 12 IA children and 3 out of 8 MIA children had hypogammaglobulinemia ($p = 0.7$). Three out of 10 IA patients and 3 out of 5 MIA children had frequent bacteremia (≥5/year). Eight children (6 IA and 2 MIA) underwent intestinal and/or liver transplant; MIA children had a worse posttransplant outcome.
Conclusions: IA children may have an immunodeficiency and associated infectious complications requiring hospitalization. We suggest performing immunologic evaluation not only in MIA but also in IA children presenting to an intestinal rehabilitation program to identify immunodeficiency. Early immunodeficiency screening may help initiate appropriate intervention and improve patient outcomes.
Level of evidence: Level III.

Intestinal atresia is a congenital malformation of the intestine that results in a narrowing or obstruction of the lumen before birth. The pathophysiology is thought to be because of vascular disruption leading to ischemic necrosis of the fetal intestine in jejunoileal atresia [1]. The prognosis for children with intestinal atresia has been improving related to multiple factors, including individualized administration of parenteral nutritional support, novel surgical lengthening procedures, and advances in intestinal transplantation.

Previous studies have shown that patients with multiple intestinal atresia with associated immunodeficiency had a poor prognosis related to infectious complications early in life [2–6]; they also had a worse posttransplant outcome, with significant risk for graft-versus-host disease (GVHD) following intestinal transplantation [7]. However, there is little known about whether there are any differences in immune function between children who have isolated intestinal atresia and those with multiple intestinal atresia, and how such differences may be associated with infectious complications and patient outcomes. The present study aimed to compare the immune function among children with multiple intestinal atresia and those with isolated intestinal atresia, and further investigate its impact on infectious complications requiring hospitalization and patient outcomes.

Abbreviations: CD, cluster of differentiation; GVHD, graft-versus-host disease; IA, isolated intestinal atresia; ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification; Ig, immunoglobulin; MIA, multiple intestinal atresia.

☆ Sources of funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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https://doi.org/10.1016/j.jpedsurg.2020.05.036
0022-3468/

1. Methods

1.1. Study population and data collection

This single-center retrospective cohort study was approved by our Institutional Review Board. We included all children aged 19 years or younger with a diagnosis of intestinal atresia, who had been referred to our intestinal rehabilitation and intestinal transplantation program from January 2000 to December 2016 for evaluation of intestinal failure and possible intestinal transplantation. Patients with a diagnosis of intestinal atresia were identified from electronic medical records based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnoses. Children with only duodenal atresia were excluded. Clinical data were collected for patient's age at the time of evaluation, gender, ethnicity, associated anomalies, surgical intervention, type of transplant if performed, and numbers of hospitalization associated with bacteremia, pneumonia, acute gastroenteritis, and urinary tract infection. Laboratory data were collected for complete blood count, immunologic work-up, and genetic test if available. Immunologic work-up at the time of evaluation included serum immunoglobulin (Ig) levels (IgG, IgM, IgA) to screen for humoral immunodeficiency and flow cytometry (including clusters of differentiation [CD] 3, 4, 8, 19, and 56) to evaluate for cellular immunodeficiency. Of note, when clinically indicated, patients underwent endoscopic evaluation with biopsy and small bowel fluid aspirate at the time of evaluation to evaluate for intestinal inflammation and small intestinal bacterial overgrowth. Patients with small intestinal bacterial overgrowth (defined as greater than 10^5 colony-forming units of bacteria per mL of luminal aspirate) were treated with oral antibiotic cycling based on susceptibilities.

1.2. Definitions

Patients were categorized into two groups based on their intestinal narrowing parts: [8] isolated intestinal atresia (IA, either jejunal or ileal atresia) and multiple intestinal atresia (MIA, if the patient had more than one area of atresia). Immunoglobulin levels and flow cytometry were classified into low and normal–high according to the reference levels by age [9]. Bacteremia was defined as identified positive blood culture. Patients were classified to have frequent bacteremia when they had an average of more than or equal to 5 episodes of bacteremia per year.

1.3. Statistical analysis

Data were analyzed using SPSS version 25.0 (Chicago, IL, USA) and SAS University Edition (SAS Institute, Cary, NC, USA), and were reported as the median (interquartile range [IQR]), or percentage. Groups of IA and MIA patients were compared using chi-square test or Fisher's exact test for categorical variables and using Mann–Whitney test for continuous variables, as appropriate. A p-value of less than 0.05 was considered as the level of significance for all tests.

2. Results

2.1. Patient characteristics

Among 91 children with intestinal atresia identified during the study period, sixty-four patients were excluded owing to duodenal atresia ($n = 16$) or lack of anatomy information to classify them into the groups ($n = 48$). The remaining patients were classified into IA ($n = 18$) and MIA ($n = 9$). There was no significant difference in the patient's age at the time of evaluation, gender, ethnicity, and the median duration of follow-up between the groups (Table 1). One MIA patient had associated tetralogy of Fallot; none had associated thymus or other malformations.

Table 1
Clinical characteristics of patients with intestinal atresia.

	Isolated intestinal atresia ($n = 18$)	Multiple intestinal atresia ($n = 9$)	P-value
Age at evaluation (years), median (IQR)	0.4 (0.8)	1.2 (1.9)	0.6
Female, *n* (%)	13 (72.2)	3 (33.3)	0.1
Ethnicity, *n* (%)			1.0
White	8 (44.4)	4 (44.4)	
Nonwhite	10 (55.6)	5 (55.6)	
Duration of follow-up (years), median (IQR)	0.9 (3.6)	1.5 (4.8)	0.5
Associated anomalies, *n* (%)			n/a
Chromosomal abnormality	0	1/9 (11.1)	
Cardiac malformation	0	1/9 (11.1)	
STEP procedure, *n* (%)	8/13 (61.5)	4/6 (66.7)	1.0

IQR, interquartile range; STEP, serial transverse enteroplasty procedure.

2.2. Immunologic work-up

Complete blood count was available in all patients at the time of evaluation. The median absolute neutrophil and lymphocyte counts (per mm^3) were 2500 and 2600 in MIA children, compared to 4650 ($p = 0.2$) and 3700 ($p = 0.1$) in IA children, respectively.

Flow cytometry was available in 21 patients (12 IA and 9 MIA). Fig. 1 compares the absolute CD counts between IA and MIA children. When these CD counts were categorized into low and normal–high based on the normal values by age, more than half of the patients had several CD counts in the low category in both IA and MIA groups: CD3 58.3% vs. 66.7% ($p = 1.0$), CD4 50.0% vs. 66.7% ($p = 0.7$), CD8 67.7% vs. 88.9% ($p = 0.3$), CD19 25.0% vs. 33.3% ($p = 1.0$), CD56 25.0% vs. 44.4% ($p = 0.4$), respectively (Table 2).

Complete immunoglobulin work-up was available in 20 patients (12 IA and 8 MIA). The median IgG, IgM, and IgA levels in MIA children were 443 g/dL, 53 g/dL, and 32 g/dL, compared to 344 g/dL, 71 g/dl, and 21 g/dL in IA children, respectively (Fig. 2). When the levels were categorized into low and normal–high based on the normal values for age, 6 out of 12 (50%) IA children, and 3 out of 8 (38%) MIA children had low IgG levels (Table 2).

Of note, among 48 patients with a referral diagnosis of intestinal atresia, who were excluded owing to a lack of anatomy information to classify them into the groups of IA or MIA, 26 children had flow cytometry, and 35 children had immunoglobulin work-up available at the time of evaluation. When the CD counts and IgG levels were categorized into low and normal–high based on the normal values by age, approximately one-third of these patients had CD counts and IgG levels in the low category: CD3 34.6%, CD4 42.3%, CD8 46.2%, CD19 24.0%, CD56 42.3%, and IgG level 34.3%.

2.3. Impact of immune function on infectious complications

Table 3 compares infectious complications between IA and MIA children. Among the patients who developed bacteremia, 3 out of 10 IA patients and 3 out of 5 MIA patients met the definition of frequent bacteremia. All but one patient in each group had a central line, although data were available only for 12 patients. There was no statistically significant correlation between Ig levels by age or CD counts by age and the presence of infectious complications in either group (data not shown). However, among the patients who presented with any type of infectious complications, 4 out of 9 children in the IA group had low IgG levels versus 1 out of 4 children in the MIA group. Similarly, among those presented with infectious complications, at least one-fourth of children had low CD counts in both IA and MIA groups: CD3 and CD4 5/8 vs. 2/4, CD8 6/8 vs. 3/4, CD19 2/4 vs. 1/4, and CD56 3/8

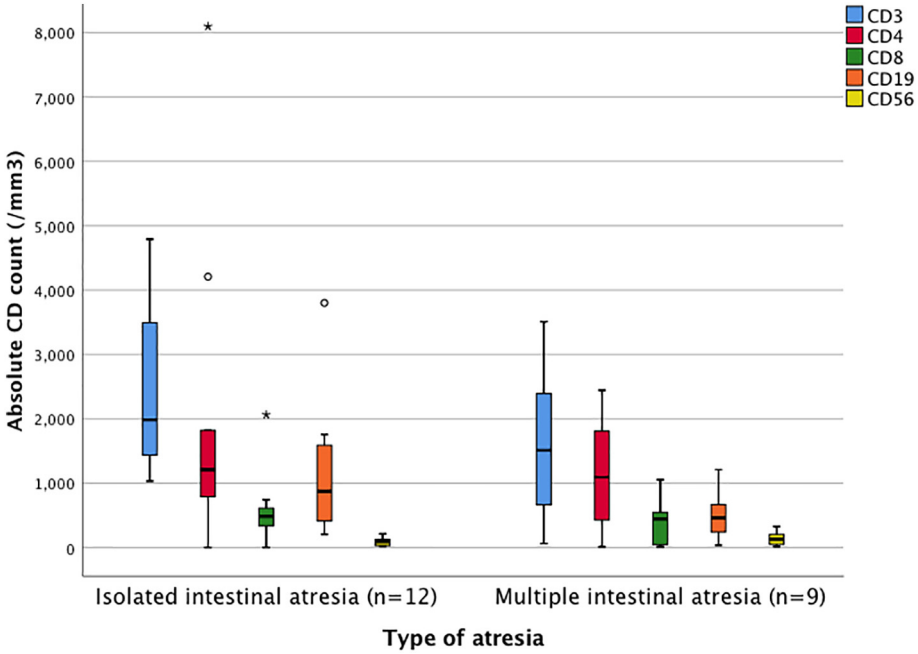

Fig. 1. Distribution of absolute CD counts by the type of intestinal atresia.

vs. 4/4, respectively. Moreover, among the patients who had frequent bacteremia, 1 out of 3 patients in each group had low IgG levels, whereas all IA and MIA patients had low CD3, CD4, and CD8 counts.

2.4. Impact of immune function on transplant outcome

Eight patients with intestinal atresia (6 IA and 2 MIA children) underwent solid organ transplant. In the IA group, one patient received an isolated small bowel transplant, one patient received an isolated liver transplant, and four patients received a combined liver-small bowel transplant, whereas both MIA patients received a combined liver-small bowel transplant. Immunoglobulin G levels were available in 6 patients before the transplant: 4 in the IA group and 2 in the MIA group. Two patients in the IA group had low IgG levels for age, whereas the other two had normal levels. Both patients in the MIA group had low IgG levels.

Flow cytometry results were available in 7 patients: 5 in the IA group and 2 in the MIA group. Four out of 5 patients in the IA group had low CD3 counts for age, whereas the CD3 counts were low in both MIA patients. Three out of 5 IA patients and both MIA children had low CD4 counts for age. All patients in the IA and MIA groups had low CD8 counts.

All transplant recipients in the IA group were alive at the end of follow-up. Only one IA patient who received a liver-small bowel transplant had two episodes of gastroenteritis after transplantation. In the MIA group, one patient deceased at 5 days after transplantation owing to subarachnoid hemorrhage and profound global hypoxic–ischemic brain injury (unrelated to MIA), and the other patient had frequent episodes of sepsis, frequent urinary tract infections and gastroenteritis but was alive and had no GVHD. Of note, among three IA children who developed acute intestinal rejection, one patient with isolated intestinal transplant required explantation of the small bowel graft owing to severe intestinal graft rejection and subsequently received a secondary liver-small bowel transplant. None of the patients developed chronic intestinal rejection during the follow-up.

Table 2
Immunologic evaluation in patients with intestinal atresia.

	Isolated intestinal atresia ($n = 12$)	Multiple intestinal atresia ($n = 9$)	P-value
Flow cytometry (CD counts) by age[a]			
CD3, *n* (%)			1.0
Low	7 (58.3)	6 (66.7)	
Normal–high	5 (41.7)	3 (33.3)	
CD4, *n* (%)			0.7
Low	6 (50.0)	6 (66.7)	
Normal–high	6 (50.0)	3 (33.3)	
CD8, *n* (%)			0.3
Low	8 (67.7)	8 (88.9)	
Normal–high	4 (33.3)	1 (11.1)	
CD19, *n* (%)			1.0
Low	3 (25.0)	3 (33.3)	
Normal–high	9 (75.0)	6 (66.7)	
CD56, *n* (%)			0.4
Low	3 (25.0)	4 (44.4)	
Normal–high	9 (75.0)	5 (55.6)	
Immunoglobulin (Ig) levels by age[b]			
IgG, *n* (%)			0.7
Low	6 (50.0)	3 (37.5)	
Normal–high	6 (50.0)	5 (62.5)	
IgM, *n* (%)			1.0
Low	2 (16.7)	2 (25.0)	
Normal–high	10 (83.3)	6 (75.0)	
IgA, *n* (%)			1.0
Low	2 (16.7)	2 (25.0)	
Normal–high	10 (83.3)	6 (75.0)	

[a] Flow cytometry results were available in 12 IA and 9 MIA children.
[b] Immunoglobulin levels were available in 12 IA and 8 MIA children.

3. Discussion

The present study is the first to describe the immunologic status and infectious complications in children with intestinal atresia who were referred for evaluation of intestinal failure and compare them between children with isolated and multiple intestinal atresia. Immune work-up in our cohort has shown that 67% and 50% of the IA patients had lymphopenia/low CD counts and hypogammaglobulinemia, respectively, and more than half of the MIA patients had lymphopenia/low CD counts. Moreover, all patients in both groups who had frequent bacteremia had low CD counts based on flow cytometry, indicating the need for immunologic work-up not only in MIA but also in IA patients.

These findings underline the importance of immunologic work-up in patients with intestinal atresia who are referred for evaluation of

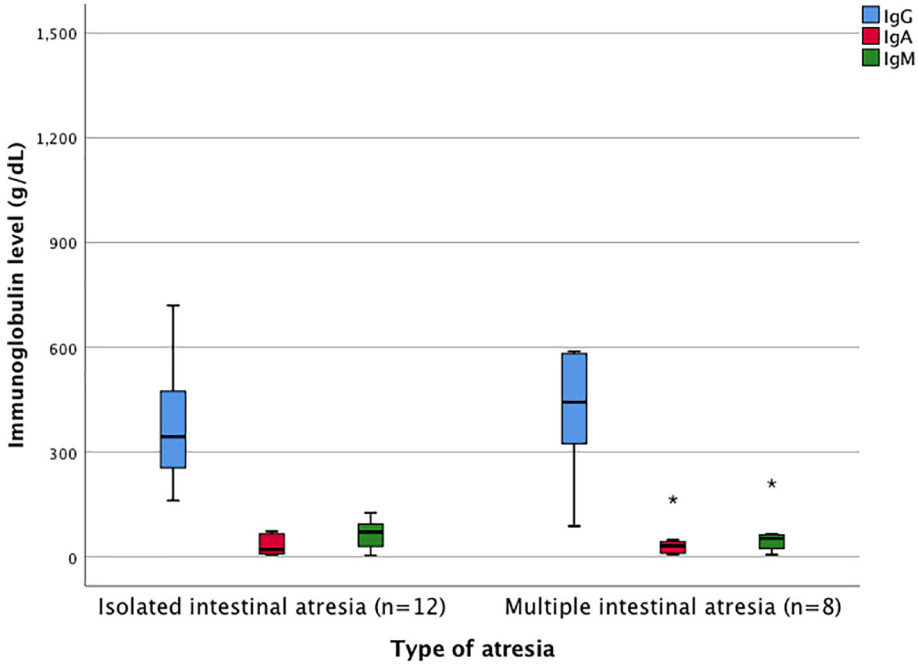

Fig. 2. Distribution of immunoglobulin (Ig) levels by the type of intestinal atresia.

intestinal failure. Prior studies have identified a correlation between MIA and immunodeficiency [2–7,10,11], but little is known about immunodeficiency in patients with isolated intestinal atresia. Moreno et al. [2] first reported an association between MIA and immunodeficiency in 1990. The authors described three siblings with MIA, two of whom had the clinical courses that strongly suggested a congenital immunodeficiency syndrome; the other sibling also had a severe combined immunodeficiency syndrome. The parents of these siblings were nonconsanguineous and healthy. Walker et al. [3] in 1993 and Rothenberg et al. [4] in 1995 also reported two cases of a syndrome involving immunodeficiency and MIA. In 1998, Lambrecht and Kluth [5] reported a patient who had MIA associated with immunodeficiency and also reviewed 35 cases of hereditary multiple intestinal atresia, a presumed autosomal recessive disorder, which is an unusual and rare form of recurrent intestinal atresia; five of those had immunodeficiency. In 2011, Ali et al. [6] reported two siblings with hereditary multiple intestinal atresia and severe combined immunodeficiency syndrome, whose parents were first-degree cousins with no family history of any significant illness. The infants were never able to tolerate enteral feeds, remained dependent on total parenteral nutrition, had repeated episodes of sepsis and died after a very difficult neonatal intensive care course.

In contrast to a previous study demonstrating that children with MIA-associated immunodeficiency were more likely to experience severe GVHD following small bowel transplant [7], none of the two MIA children who underwent a combined liver–small bowel transplant in the present cohort developed GVHD during the follow-up, even though both were found to have low CD counts and hypogammaglobulinemia.

Table 3
Infectious complications requiring hospitalization in patients with intestinal atresia.

	Isolated intestinal atresia ($n = 18$)	Multiple intestinal atresia ($n = 9$)	P-value
Bacteremia, *n* (%)	10 (55.6)	5 (55.6)	0.7
Pneumonia, *n* (%)	5 (27.8)	0 (0.0)	0.1
Acute gastroenteritis, *n* (%)	6 (33.3)	2 (22.2)	0.7
Urinary tract infection, *n* (%)	2 (11.1)	0 (0.0)	0.5

This observation might reflect a small number of MIA patients undergoing transplant in the present cohort and a short posttransplant follow-up time (one MIA patient died at 5 days following the transplant). However, advances in posttransplant care, along with vigilance about avoiding overimmunosuppression in patients with underlying immunodeficiency, might help decrease the incidence of GVHD. Additionally, although more than half of the patients in the IA group who received transplantation had immunodeficiency, they did not experience frequent infectious complications after transplantation as compared to children in the MIA group. A further larger-scale study might look into whether the type of intestinal atresia itself is a contributing factor for having a worse posttransplant outcome, in addition to immunodeficient status.

Limitations of the present study were mainly related to its retrospective nature. Half of the patients we identified as having intestinal atresia were excluded owing to a lack of anatomy information to classify them into the groups, and data collection was also limited and missing on the history of infectious complications that occurred at the referral hospitals or clinics. However, even in this unclassified group, available immunologic work-up has shown that approximately one-third of these patients had low CD counts and low IgG levels. Additionally, since immunologic work-up was not routinely performed in all patients with IA at the time of evaluation, the lack of immunologic data in the IA group could have an impact on the true prevalence of immunodeficiency that we reported in this study. Moreover, immunologic work-up was not routinely performed in all children with short-bowel syndrome who were referred to our intestinal rehabilitation program, and therefore, we were unable to retrospectively compare the immune function of children with short-bowel syndrome owing to intestinal atresia versus other etiologies (such as necrotizing enterocolitis, malrotation with volvulus, etc.). Furthermore, although previous studies linked the immunodeficiency in MIA to a mutation in the tetratricopeptide repeat domain 7A (TTC7A) gene [6,10–12], we could not confirm this association in our MIA patients owing to a lack of genetic data. Finally, since most of our patients were referred for evaluation of intestinal failure and possible intestinal transplantation, the present study might be subject to selection bias, which could be overcome by a multicenter study of patients with various types of intestinal atresia. A prospective, larger-scale study examining functional immunologic evaluation (i.e., functional T cell studies and

measurements of antibody response to vaccines) in IA children as well as in a control group with equivalent nutritional background and different types of surgical history might be warranted to explore further the association between intestinal atresia and immunodeficiency.

In conclusion, our findings have shown that IA children who were referred for evaluation of intestinal failure could also have immunodeficiency and associated infectious complications requiring hospitalization. It might be beneficial to perform immunologic evaluation not only in patients with multiple intestinal atresia, but also in those with isolated intestinal atresia who are referred to the intestinal rehabilitation program to identify immunodeficiency. A diagnosis of immunodeficiency may help facilitate early infectious work-up for any febrile illnesses in these patients as well as could have an impact on the management of patients with central lines for parenteral nutrition or the posttransplant prophylactic management for those undergoing transplantation. We suggest that IA children with immunodeficiency who has a central line should receive empiric antibiotic treatment for any febrile illnesses while awaiting sepsis work-up to avoid progression to overwhelming sepsis. For those with underlying immunodeficiency undergoing transplantation, balancing the immunosuppression level is a key challenge. The immunosuppressive regimen should be tailored in these patients to minimize the risk of allograft rejection while avoiding overimmunosuppression that might put them at higher risk for infections (especially in those undergoing liver-small bowel transplant with concurrent splenectomy who are particularly at risk for life-threatening pneumococcal infections), posttransplant lymphoproliferative disorder, and GVHD. Early immunodeficiency screening with flow cytometry and serum immunoglobulin levels and further referral to an immunologist for functional immunologic evaluation may help initiate appropriate intervention and improve patient outcomes. Future studies should gear toward a larger number of patients in a multicenter setting to further investigate the association between immunodeficiency and intestinal atresia as well as to examine the long-term outcome of patients with intestinal atresia who have and do not have immunodeficiency.

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