

ORIGINAL ARTICLE

Neonatal isolated rectal bleeding and the risk of hypersensitivity syndromes

O Reiter, I Morag, R Mazkereth, T Strauss and A Maayan-Metzger

OBJECTIVE: When rectal bleeding occurs in an otherwise asymptomatic child, it can be classified as isolated rectal bleeding (IRB). Among the different etiologies suggested for IRB, one of the most common is a hypersensitivity reaction of the bowel mucosa to digested antigens. The objective of this study was to assess the long-term outcomes and the risk of developing hypersensitivity syndromes among infants following an IRB event.

STUDY DESIGN: A historical prospective comparative study was carried out. The study compared 77 infants who were born at the Sheba Medical Center in Israel during the period 2002 to 2009 and who experienced a neonatal IRB event to 77 infants with the same gestational age, but without IRB. Data were obtained from hospital records and from phone interviews with the parents regarding hypersensitivity syndrome between the ages of 3 and 10 years.

RESULT: The IRB group was not at an increased risk of developing a hypersensitivity syndrome or gastrointestinal symptoms compared to the control group. Longer duration of breast-feeding was found to be related to a lower incidence of hypersensitivity symptoms.

CONCLUSION: An IRB event in the neonatal period does not increase the risk of developing hypersensitivity syndromes or food allergies during childhood.

Journal of Perinatology advance online publication, 10 October 2013; doi:10.1038/jp.2013.129

Keywords: infants; allergy; asthma; atopic dermatitis; allergic rhinitis

INTRODUCTION

Infantile rectal bleeding is an alarming clinical sign that requires additional investigation. When rectal bleeding occurs in an otherwise asymptomatic child, it can be classified as isolated rectal bleeding (IRB), with an estimated incidence of 0.37% among newborn infants.^{1,2}

Several etiologies have been suggested for IRB.^{3,4} In the past, the most common etiology was believed to be a hypersensitivity reaction of the bowel mucosa to digested antigens, primarily to the protein in cow's milk. Studies conducted in the late 1990s showed that eliminating cow's milk from an infant's diet was followed by cessation of the bleeding. However, reintroducing cow's milk into infants' diets did not result in recurrence of the bleeding.⁵

Studies aimed at evaluating the involvement of allergic mechanisms among infants with rectal bleeding have shown varying results.^{6–9}

More recent studies have demonstrated a relatively low rate (12.5 to 18%)^{6,7} of evidence to support allergic colitis among infants with IRB. These studies found IRB to be a benign and self-limiting phenomenon whose cause is mostly unknown. Still, some of the infants who have experienced an IRB event are given specific dietary restrictions that might impair their childhood nutrition. The long-term incidence of allergic clinical signs among these infants has not been evaluated extensively.

The aim of this study is to assess the long-term outcomes regarding the risk of developing hypersensitivity syndrome and/or gastrointestinal symptoms during childhood among infants who experienced an IRB event during the neonatal period.

METHODS

Sample and setting

Medical charts were surveyed and reviewed for all term and preterm neonates born at the Sheba Medical Center between 1 January 2002 and 31 December 2009, and who subsequently experienced rectal bleeding during their stay in the hospital's nursery. For the purposes of this study, IRB is defined as any overt rectal bleeding without hematemesis or any other clinical manifestations, such as a distended or tender abdomen, apathy, sick-looking baby and apnea or bradycardia. In addition, only infants with normal abdominal X-rays were included in the study. Exclusion criteria included infants with another active disease concurrent to their IRB, such as polycythemia, perinatal asphyxia, severe thrombocytopenia or coagulation disturbances. Infants with major congenital malformations were also excluded.

Data were collected in two steps:

(1) Postnatal information was gathered through the Sheba Medical Center's archives and medical charts. Data recorded included: gender, gestational age (GA), birth weight, small or appropriate for GA, delivery mode, multiple pregnancy, feeding type (breast-fed or formula-fed) and day of discharge from the nursery.

(2) Early childhood information was obtained through telephonic interviews with the parents of the children, who ranged in age from 3 to 10 years. Data recorded included: duration of breast-feeding, type of baby formula feeding, age at which the baby was exposed to formula and cow's milk, presence of gastrointestinal complaints (constipation, diarrhea and abdominal pain), recurrence of bloody stools, history of hospital admissions, food, milk or drug allergy, history of wheezing or asthma, history of atopic dermatitis, history of allergic rhinitis and number of atopic siblings.

For the purposes of this study, we defined hypersensitivity syndrome as the presence of at least one of the following in the child: asthma after the age of 3, atopic dermatitis or allergic rhinitis.

Of the 120 newborns presenting with IRB in the nursery during the study period, 22 fell into the definitions for the exclusion criteria and were not included in the study. Moreover, 21 parents declined to give their consent for participation. Thus, the final study group consisted of 77 children. For each child in the study group, a child born on a proximal date with the same GA was matched and recruited for the non-IRB control group. These 77 children did not experience an IRB event during perinatal hospitalization but were subject to the same rules for inclusion and exclusion in the study as the children in the study group. The medical charts of the control group were reviewed for the same demographic data, and the early childhood interview information was obtained in the same manner as for the study group.

This study was approved by the Sheba Medical Center Ethics (Helsinki) Committee.

Statistical analysis

After all the information was gathered, each group was divided into two subgroups: (a) preterm babies with a GA of ≤ 34 weeks and (b) late preterm and term babies with a GA of ≥ 35 weeks.

All data for each subgroup in the study population were compared to the data for the matching subgroup in the control population. Categorical data are summarized as frequencies and percentages; numeric data are summarized as medians and interquartile ranges. Chi-square testing was used to examine associations between categorical data and the Mann-Whitney test was used for numeric data. A multivariate analysis was conducted for parameters from the univariate analysis, with a P value ≤ 0.2 through logistic regression. Statistical significance was considered to be a P value < 0.05 . All analyses were performed using SPSS version 21 (SPSS Chicago, IL, USA).

RESULTS

Both the study and the control groups included 53 children who were born at late preterm or term ('term subgroup' GA ≥ 35 weeks) and 24 children who were born preterm ('preterm subgroup' GA ≤ 34 weeks).

Postnatal period

Table 1 compares the postnatal data for infants who experienced an IRB event with data from the control group divided into two subgroups: (1) term and late preterm and (2) preterm. These groups were similar with regard to GA, birth weight and gender. More infants in the study group (IRB⁺) were defined as small for their GA, and the infants in this group were hospitalized for a longer duration.

Long-term follow-up

Table 2 compares the long-term follow-up of the study group to that of the control group.

No differences were recorded between the study groups (term and late preterm; preterm) and the corresponding control groups with regard to all gastrointestinal symptoms or allergic

manifestations (food and drug allergy, asthma, allergic dermatitis or allergic rhinitis).

In the term and late preterm subgroup, children who had experienced a neonatal IRB event exhibited a greater chance of experiencing an additional bloody stool event compared with children who had not experienced such an event. However, these children were not at a higher risk of experiencing two or more additional bloody stool events.

Recurrent hospitalizations were recorded among seven children in the term and late preterm study subgroup (respiratory disease, arthritis, hernia and tonsillectomy), less than among the corresponding control subgroup. In the preterm study subgroup, five children were hospitalized (pneumonia, bronchiolitis, diarrhea, hernia and tympanotomy) with no significant differences compared with their matched control subgroup.

Hypersensitivity syndrome

For the purpose of examining the risk factors of developing hypersensitivity symptoms and ruling out possible confounders, a group of hypersensitive children was defined. This group consisted of all the children participating in the study (study and control groups) who exhibited at least one of the following symptoms: asthma after the age of 3, allergic dermatitis or allergic rhinitis. The rest of the children were defined as non-hypersensitive. The results of the comparison between the hypersensitive group and the non-hypersensitive group are depicted in Table 3.

Children with hypersensitivity symptoms had a lower GA and birth weight compared with the non-hypersensitive group. In addition, they had a shorter duration of breast-feeding and, consequently, were exposed to baby formula at a younger age. History of a neonatal IRB event was not found to be significantly higher among children who developed hypersensitive symptoms in their early childhood.

The logistic regression showed that no single parameter, including history of IRB, GA, birth weight, small for GA, duration of breast-feeding or age at formula exposure, was linked to a higher risk of developing hypersensitivity symptoms during early childhood.

DISCUSSION

The purpose of the current study was to evaluate whether newborn infants presenting with IRB are at a higher risk of developing hypersensitivity syndromes and/or gastrointestinal symptoms during early childhood. No evidence was found for an increased risk among these infants.

Several studies have described the benign and self-limiting nature of an IRB event during infancy,^{5–8} yet there has been no evaluation of the long-term outcomes, morbidity or hypersensitivity profile of these infants during their later childhood.

Table 1. Data from study group and controls in the postnatal period divided into two subgroups: term and late preterm subgroup and preterm subgroup

	Term and late preterm			Preterm		
	IRB (n = 53)	No IRB (n = 53)	P value	IRB (n = 24)	No IRB (n = 24)	P value
Gestational age (weeks)	37 (36–39)	37 (36–39)	0.946	33 (32–34)	33 (32–34)	1.000
Birth weight (g)	2905 (1905–3270)	2777 (2609–3253)	0.280	1487 (1215–1780)	1795 (1565–2071)	0.022
SGA	15 (28.3%)	2 (3.8%)	0.001	10 (42%)	3 (12.5%)	0.023
Male/female ratio	60%/40%	47%/53%	0.173	54%/46%	50%/50%	0.770
Discharge date	10 (7–19)	2.5 (2–4)	<0.001	39 (24–47)	27 (16–38)	0.056

Abbreviations: IRB, isolated rectal bleeding; SGA, small for gestational age.

Categorical data are summarized as frequencies (percentages); numerical data are summarized as medians (interquartile ranges).

Table 2. Long-term follow-up data from study group and controls divided into term and late preterm subgroup and preterm subgroup

	Term and Late preterm			Preterm		
	IRB (n = 53)	No IRB (n = 53)	P value	IRB (n = 24)	No IRB (n = 24)	P value
Age at interview (years)	4.6 (3.65–6.05)	7.4 (4.65–8.25)	< 0.001	4.6 (3.77–6.82)	6.6 (5.02–7.67)	0.009
Duration of breast-feeding (months)	3 (0–8)	4 (0–10)	0.420	3 (0–6)	1.25 (0–6)	0.458
Age at cow's milk exposure (months)	12 (8–12)	10 (7.5–12)	0.406	12 (6–12)	12 (8–12)	0.947
History of gastrointestinal complaints	6 (11.4%)	4 (7.6%)	0.506	2 (8.3%)	3 (12.5%)	1.000
Patients with recurrent bloody stool	7 (13.2%)	0 (0%)	0.013	1 (4.2%)	0 (0%)	1.000
Patients with more than one additional bloody stool event	3 (5.7%)	0 (0%)	0.243	0 (0%)	0 (0%)	NA
History of hospitalization	7 (13.2%)	16 (30.2%)	0.034	5 (20.8%)	11 (45.8%)	0.066
Patients with food allergy	2 (3.8%)	0 (0%)	0.495	4 (16.7%)	0 (0.0%)	0.109
Patients with milk allergy	1 (1.9%)	2 (3.8%)	1.000	1 (4.2%)	0 (0%)	1.000
Patients with drug allergy	4 (7.5%)	2 (3.8%)	0.678	0 (0%)	2 (8.3%)	0.489
Wheezing before age of 3	14 (26.4%)	14 (26.4%)	1.000	9 (37.5%)	12 (50%)	0.383
Asthma after the age of 3	5 (9.4%)	4 (7.5%)	1.000	5 (20.8%)	5 (20.8%)	1.000
Atopic dermatitis	7 (13.2%)	5 (9.4%)	0.540	3 (12.5%)	2 (8.3%)	1.000
Allergic rhinitis	4 (7.5%)	4 (7.5%)	1.000	2 (8.3%)	7 (29.2%)	0.137
Percentage of allergic siblings	0 (0–0%)	0 (0–42%)	0.254	0 (0–50%)	0 (0–50%)	0.949
Patients with any atopic symptom	12 (22.6%)	16 (30.2%)	0.378	10 (41.7%)	11 (45.8%)	0.771

Abbreviation: IRB, isolated rectal bleeding.

Categorical data are summarized as frequencies (percentages); numerical data are summarized as medians (interquartile ranges).

Table 3. Hypersensitive and non-hypersensitive groups

	Hypersensitive (N = 49)	Non-hypersensitive (N = 105)	P value
IRB	22 (44.9%)	55 (52.4%)	0.387
Gestational age (weeks)	36 (32–38)	37 (34–38)	0.018
Birth weight (g)	2030 (1548–2877)	2582.5 (1885–3041)	0.033
SGA	9 (18.4%)	21 (20.2%)	0.791
Male/female ratio	59.2%/40.8%	50.5%/49.5%	0.313
Feeding			
Exclusively breast-fed	11 (22.4%)	18 (17.3%)	0.112
Exclusively formula-fed	18 (36.7%)	25 (24%)	
Combined feeding	20 (40.8%)	61 (58.7%)	
Long-term follow-up			
Age at interview (years)	6 (4.25–7.35)	5.5 (4.1–7.5)	0.764
Duration of breast-feeding (months)	1 (0–6)	4 (0.5–8)	0.018
Age at formula exposure (months)	0 (0–2.5)	1 (0–5.75)	0.005
Age at cow's milk exposure (months)	12 (8–12)	12 (7.75–12)	0.161
Patients complaining of constipation	2 (4.1%)	3 (2.9%)	0.654
Patients complaining of abdominal pain	3 (6.1%)	6 (5.7%)	1.000
Patients complaining of diarrhea	1 (2%)	2 (1.9%)	1.000
Patients with recurrent bloody stool	3 (6.1%)	5 (4.8%)	0.710
Hospitalization			
History of emergency hospitalization	11 (22.4%)	15 (14.3%)	0.451
History of elective hospitalization	4 (8.2%)	9 (8.6%)	
Percentage of allergic siblings	0 (0–50%)	0 (0–0%)	0.087

Abbreviations: IRB, isolated rectal bleeding; SGA, small for gestational age.

Categorical data are summarized as frequencies (percentages); numerical data are summarized as medians (interquartile ranges).

Although the data for the current study were based on the subjective replies of parents to telephone interviews, they provide sufficient information regarding the morbidity of these children and their hypersensitivity profiles during early childhood.

The differential diagnosis for rectal bleeding in infancy includes several different mechanisms. Etiologies such as necrotizing enterocolitis and midgut volvulus are serious and life-threatening conditions, but are not part of the differential diagnosis for IRB since they have a very different clinical correlation (sick-looking child, pain, pathological abdominal x-rays so on).^{3,4} Hirschsprung's disease and blood clotting disorders may manifest as IRB, yet

additional symptoms are highly likely. In addition, the duration of the bleeding is expected to be longer than seen in typical IRB cases. Anal fissures and maternal blood digestion remain a differential diagnosis for an IRB event, but can be excluded with a simple physical examination of either the infant (anal fissure) or the mother.

Two mechanisms have been suggested to be the main etiologies for IRB in newborn infants: infectious and immunologic.

Arvola *et al.*⁶ examined the clinical, allergic and microbiologic properties of infants with rectal bleeding. They found that these infants had a lower concentration of Bifidobacteria and

Lactobacilli in their feces compared with the control group. Kumagai et al.¹⁰ recorded a higher concentration of pathogenic enterobacteria, such as *Klebsiella*, among infants with IRB. These studies support a finding described in a previous study by our group² showing that non-breast-fed infants have a higher rate of IRB. It has also been shown that infants with low birth weight have a delayed colonization of their intestinal flora with *Bifidobacterium* compared with normal full-term infants.¹¹ Indeed, the current study found a significant correlation between low birth weight and a risk of developing IRB.

Eosinophilic allergic colitis or food protein-induced proctocolitis is a condition in which the bowel mucosa reacts with inflammation when exposed to foreign proteins, most commonly cow's milk protein. In the past, this allergic reaction was thought to be the most common etiology causing IRB in newborns. In 2005 Xanthakos et al.⁸ showed that 64% of infants with an IRB event exhibited tissue evidence of allergic colitis. Yet more recent studies have provided evidence for allergic colitis in only 12.5 to 18%^{6,7} of all infants with IRB. Furthermore, a study that examined gene expression in bowel biopsy samples from infants with IRB did not find any evidence of an allergic mechanism at the cellular level.⁹

In the current study, infants with IRB did not exhibit a higher rate of clinical signs for food and drug allergies or any other hypersensitivity symptoms (defined as asthma, atopic dermatitis or allergic rhinitis) in their early childhood compared with the control group. This supports the notion that the etiology of IRB is not an allergic mechanism.

It should be mentioned, however, that an allergic non-immunoglobulin E-mediated reaction, such as allergic colitis, may be the mechanism for early IRB and will not be reflected later in childhood as a hypersensitivity syndrome.

While looking for risk factors for hypersensitivity symptoms among the study population, we found that an earlier GA and a shorter period of breast-feeding were correlated with a higher risk of such symptoms. In the univariate analysis we found that children with hypersensitivity symptoms had a significantly shorter duration of breast-feeding compared with the non-hypersensitive children. Several studies have examined the impact of breast-feeding on the development of hypersensitivity syndromes. A 2001 meta-analysis compared the incidence of atopic dermatitis in breast-fed infants with the incidence among formula-fed infants and found a protective effect resulting from exclusive breast-feeding for a period of 3 months.¹² An additional 2001 meta-analysis found that breast-feeding exclusively for at least 3 months had a protective effect against the development of asthma,¹³ although a 2002 Cochrane review found no protective effect from exclusive breast-feeding beyond those 3 months.¹⁴ In a policy statement, the American Academy of Pediatrics¹⁵ stated that there was evidence that breast-feeding for at least 4 months, as opposed to feeding with formula made from intact cow milk protein, prevented or delayed the occurrence of atopic dermatitis, cow milk allergy and wheezing in early childhood.

The second difference found to be significant in the univariate but not in the multivariate analysis was the GA. Children who experienced hypersensitivity symptoms were born at an earlier GA compared with their peers. Previous studies have already described this association. For example, it is known that late preterm and early-term children are at a greater risk of developing asthma during childhood compared with term children.¹⁶ In

addition, children who were born at an early birth week have a greater chance of inhaled corticosteroid use during childhood. The earlier the birth week, the greater the risk.¹⁷

In conclusion, the results of this study suggest that infants presenting with IRB are not at a higher risk of developing hypersensitivity symptoms, food and drug allergies or gastrointestinal symptoms during childhood.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

- Lawrence WW, Wright JL. Causes of rectal bleeding in children. *Pediatr Rev* 2001; **22**: 394–395.
- Maayan-Metzger A, Ghanem N, Mazkereth R, Kuint J. Characteristics of neonates with isolated rectal bleeding. *Arch Dis Child Fetal Neonatal Ed* 2004; **89**: 68–70.
- Silber G. Lower gastrointestinal bleeding. *Pediatr Rev* 1990; **12**(3): 85–93.
- Boyle JT. Gastrointestinal bleeding in infants and children. *Pediatr Rev* 2008; **29**(2): 39–52.
- Pumberger W, Pomberger G, Geissler W. Proctocolitis in breast fed infants: a contribution to differential diagnosis of haematochezia in early childhood. *Postgrad Med J* 2001; **77**(906): 252–254.
- Arvola T, Ruuska T, Keränen J, Hyöty H, Salminen S, Isolauri E. Rectal bleeding in infancy: clinical, allergological, and microbiological examination. *Pediatrics* 2006; **117**: e760–e768.
- Jang HJ, Kim AS, Hwang JB. The etiology of small and fresh rectal bleeding in not-sick neonates: should we initially suspect food protein-induced proctocolitis? *Eur J Pediatr* 2012; **171**(12): 1845–1849.
- Xanthakos SA, Schwimmer JB, Melin-Aldana H, Rothenberg ME, Witte DP, Cohen MB. Prevalence and outcome of allergic colitis in healthy infants with rectal bleeding: a prospective cohort study. *J Pediatr Gastroenterol Nutr* 2005; **41**(1): 16–22.
- Ohtsuka Y, Jimbo K, Inage E, Mori M, Yamakawa Y, Aoyagi Y et al. Microarray analysis of mucosal biopsy specimens in neonates with rectal bleeding: is it really an allergic disease? *J Allergy Clin Immunol* 2012; **129**(6): 1676–1678.
- Kumagai H, Maisawa S, Tanaka M, Takahashi M, Takasago Y, Nishijima A et al. Intestinal microbiota and secretory immunoglobulin A in feces of exclusively breast-fed infants with blood-streaked stools. *Microbiol Immunol* 2012; **56**(10): 657–663.
- Sakata H, Yoshioka H, Fujita K. Development of the intestinal flora in very low birth weight infants compared to normal full-term newborns. *Eur J Pediatr* 1985; **144**(2): 186–190.
- Gdalevich M, Mimouni D, David M, Mimouni M. Breast-feeding and the onset of atopic dermatitis in childhood: a systematic review and meta-analysis of prospective studies. *J Am Acad Dermatol* 2001; **45**(4): 520–527.
- Gdalevich M, Mimouni D, Mimouni M. Breast-feeding and the risk of bronchial asthma in childhood: a systematic review with meta-analysis of prospective studies. *J Pediatr* 2001; **139**(2): 261–266.
- Kramer MS, Kakuma R. Optimal duration of exclusive breastfeeding. *Cochrane Database Syst Rev* 2012; **8**: CD003517.
- Greer FR, Sicherer SH, Burks AW. American Academy of Pediatrics Committee on Nutrition; American Academy of Pediatrics Section on Allergy and Immunology. Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. *Pediatrics* 2008; **121**(1): 183–191.
- Goyal NK, Fiks AG, Lorch SA. Association of late-preterm birth with asthma in young children: practice-based study. *Pediatrics* 2011; **128**(4): e830–e838.
- Vogt H, Lindström K, Bråbäck L, Hjern A. Preterm birth and inhaled corticosteroid use in 6- to 19-year-olds: a Swedish national cohort study. *Pediatrics* 2011; **127**(6): 1052–1059.