Progress in Pediatric Cardiology 53 (2019) 54–58

Contents lists available at ScienceDirect

Progress in Pediatric Cardiology

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

Non–IgE-mediated gastrointestinal food-induced allergic disorders can mimic necrotizing enterocolitis in neonates with congenital heart diseases with left-ventricular outflow tract obstruction

Alessia Callegari[a,*], Sasha J. Tharakan[b], Martin Christmann[a]

[a] Pediatric Cardiology, Pediatric Heart Centre, Department of Pediatric Surgery, University Children's Hospital Zurich, Switzerland
[b] General and Thoracic Surgery, Department of Pediatric Surgery, University Children's Hospital Zurich, Switzerland

ABSTRACT

Aim: Patients with congenital cardiac disease and left-ventricular outflow tract obstruction are at high risk of necrotizing enterocolitis. However, non–IgE-mediated gastrointestinal food-induced allergic disorders might present themselves with a similar clinical picture and we believe that these clinical entities have been underestimated and could be misinterpreted as necrotizing enterocolitis. In our analysis, we highlight the increased incidence of food protein–induced enterocolitis syndrome and allergic proctocolitis, discuss their possible pathophysiological pathways and their impact on morbidity and clinical care in this patient group.

Methods and results: Twenty-four patients with left-ventricular outflow tract obstruction were included in the analysis. Six patients (25%, 3 female) showed symptoms (onset at 33 ± 21 days of age) compatible with food protein-induced allergic proctocolitis or enterocolitis syndrome. Clinical picture was inconsistent with classical necrotizing enterocolitis, nevertheless three patients received conservative treatment for a necrotizing enterocolitis. Blood cultures, C-reactive protein (< 4 mg/L ± 0) and leucocytes (9.1 ± 1G/L) were negative but relevant eosinophilia (16.6 ± 6.9%) was present in five patients. After elimination of cow milk all patients experienced symptoms resolution in 5 ± 2 days.

Conclusions: Non-IgE-mediated gastrointestinal food-induced allergic disorders can mimic necrotizing enterocolitis and need to be taken in account in well-appearing neonates with congenital heart disease and left-ventricular outflow tract obstructions presenting atypical necrotizing enterocolitis symptoms. The partially insufficient perfusion of the bowel wall due to left-ventricular outflow tract obstruction can enhance bacterial translocation and seems to be responsible for an aberrant immune response to ingested milk protein. Improving the systemic perfusion with an earlier relief of the obstruction of the left-ventricular outflow tract should be aimed for. To protect the homeostasis of the intestinal flora hydrolyzed or amino acid-based formula milk together with complementary or prophylactic strategies (such as stimulating intestinal motility or treating intestinal bacterial overgrowth) should be used.

1. Introduction

Patients with congenital heart disease (CHD) with left ventricular outflow tract (LVOT) obstruction have an increased incidence of necrotizing enterocolitis (NEC) [1]. However, non–IgE-mediated gastrointestinal food-induced allergic disorders (non-IgE-GI-FAs) might present themselves with similar signs and symptoms and could be under- or misdiagnosed in this population. Non-IgE-GI-FAs account for an unknown proportion of non-IgE mediated food allergies that last from benign proctitis to debilitating enteropathy and include, among others, food protein–induced enterocolitis syndrome (FPIES) and food protein-induced allergic proctocolitis (FPIAP) [2]. These two clinical entities result from a hypersensitivity to food antigens ingested or derived from the mother's diet and excreted in her milk. Cow milk (CM) is the most common trigger [3]. Symptoms can develop in the first weeks of life. FPIAP represents the milder end of the spectrum and remains among the common causes of hematochezia in infants (incidence 1–3%) [4]. It is characterized by intermittent bloody stools in otherwise well-appearing neonates [5]. FPIES represents its severe form and is characterized by persistent emesis or diarrhea in association with failure to thrive (FTT). The patients show a relative eosinophilia or, rarely, macrocytosis [6]. The role of eosinophils is still widely unknown [7]. On the one hand they act as antigen-presenting cells and potentiate the immune response, which can provoke tissue damage and dysfunction. On the other hand, they also have immunoregulatory functions [8]. Therefore, it remains unclear whether the eosinophilic response is directed against the antigen or is directed to promote tissue repair. Despite the potential severity at onset, non-IgE-GI-FAs have a favorable prognosis and the majority resolve in the first years of life [5]. Elimination of the allergen (normally cow's milk and soy) from the maternal diet or use of an extensively hydrolyzed/amino acid-based formula milk is usually sufficient for symptoms resolution while chronic exposure

* Corresponding author at: University Children's Hospital, Pediatric Heart Centre, Department of Surgery, Steinwiesstrasse 75, 8032 Zurich, Switzerland.
E-mail address: alessia.callegari@kispi.uzh.ch (A. Callegari).

https://doi.org/10.1016/j.ppedcard.2019.01.003
Received 29 November 2018; Received in revised form 11 January 2019; Accepted 13 January 2019
Available online 17 January 2019
1058-9813/

Table 1
Summary of patients' characteristic, clinical manifestation, laboratory analysis and course.

Baseline						Onset			Laboratory data			Consequences				
Case	PMA (wk)	Diagnose	BW (g)	Sex	ΔP (mmHg)	Age (d)	Symptoms	Milk	Eos (%)	WBC (G/L)	CRP (mg/L)	NEC-therapy[a] (y/n)	Imaging (y/n)	Onset symptoms to diet change (d)	Diet change to symptom stop (d)	Eos after symptom stop (%)
A	41	CoA	4720	M	40	14	-Haematochezia -Abdominal distension	BM	14.5	12.2	< 4	y	y	5	5	2
B	38	CoA	2260	M	35	40	-Haematochezia -Abdominal distension -Emesis	BM	27.2	9.3	< 4	n	y	4	7	5
C	36	HLHS	2440	M	/	11	-Haematochezia -Abdominal distension	BM FM	19.5	8.06	< 4	y	y	40	3	2.2
D	38	HLHS	2940	F	/	15	-Haematochezia	BM FM	18.5[b]	9.61	< 4	n	y	15	8	1.5[b]
E	39	HpA	3070	F	/	11; 28	-Haematochezia -Abdominal distension -Emesis	BM FM	9.9 10.1	12.1 8.19	< 4	y	y	28	6	1.8
F	38	AoS	3000	F	/	95	-Haematochezia -Emesis -Abdominal distension	MM	14.7	10.1	< 4	n	y	40	7	1.7

PMA: ponstmenstrual age; BW: birth weight; ΔP: a*rm-leg* pressure *gradient*; Eos: eosinophils; WBC: white blood cells; CRP: C-reactive protein; NEC: necrotizing enterocolitis; MC: milk change; CoA: coarctation of the aorta; HLHS: hypoplastic left heart syndrome; HpA: hypoplasia of aorta; AoS: aortic stenosis; BM: breast milk; FM: formula milk.

[a] NEC-therapy: sepsis work-up, bowel rest, parenteral nutrition, antibiotics (meropenem).

[b] Monocytes.

might result in FTT. Their pathophysiology has not yet been clearly defined and the diagnosis remains challenging [9]. Aim of our case series is to highlight the increased incidence of non-IgE-GI-FAs in neonates with CHD with LVOT obstructions and to discuss possible pathophysiological pathways and the impact on morbidity and treatment in this patient group.

2. Cases Presentation

Among the patients of our cardiologic unit born between January and October 2018 we identified six out of a total of 24 neonates with LVOT obstructions (aortic arch coarctation, aortic stenosis, hypoplasia or atresia) that showed symptoms compatible with FPIAP or FPIES. Characteristics of these infants are summarized in Table 1. Three of those patients presented with symptoms consistent with FPIAP while three patients experienced systemic symptoms consistent with FPIES. Symptoms, clinical courses and radiological findings were inconsistent with classic NEC, nevertheless three of the patients were treated for NEC. Sepsis work-up showed negative blood cultures and normal CRP (C-reactive protein) values but eosinophilia in five patients and macrocytosis in one. Changing to hydrolyzed formula milk and thus, eliminating CM from the diet, all patients experienced resolution of their symptoms. Exemplary, two cases are presented in more detail:

- Case A

A male term infant with a not-critical coarctation of the aorta (CoA) was delivered by a 34-year old healthy woman. At the age of two weeks the neonate showed intermittent hematochezia and a therapy-resistant diaper candidiasis without other gastrointestinal symptoms. Echocardiographic gradient in the aortic arch and pressure gradient between upper and lower extremities increased during the first weeks of life (70 mm Hg and 30 mm Hg, respectively). He was therefore hospitalized for surgical correction at the age of 28 days. Directly after admission, due to a relevant episode of bloody stool with abdominal distension, he was treated as probable NEC and planned surgery was delayed. Abdominal sonography showed little pneumatosis, while two more abdominal sonographies and x-ray in the following 48 h showed no pathological findings. Eosinophil blood count was elevated while white cell count was normal and blood cultures were negative. Two days later surgical correction (extended resection and end-to-end aortic arch anastomosis) was completed without complications and the pressure gradient normalized. After four days of bowel rest and systemic antibiotic treatment with meropenem, enteral feedings were restarted with hydrolyzed formula since FPIAP was suspected. Hematochezia, abdominal distention and feeding intolerance resolved after five days and eosinophil blood count normalized (Fig. 1A).

- Case E

A female term infant with prenatal diagnosis of double outlet right ventricle, side-by-side position of the great vessels, CoA and aortic arch hypoplasia was delivered by a 31-year old healthy woman. After seven days reconstruction of the aortic arch with pulmonary artery banding was performed without complications. At 11 days of age the neonate presented with bloody stools without any other symptoms. The episode was treated as probable NEC without radiological correlate at the time of diagnosis and the following 48 h. Blood cultures and other infection parameters were negative, while eosinophil blood count was elevated. After four days of bowel rest and five days of systemic antibiotic treatment with meropenem the symptoms disappeared and enteral feedings with breast milk and formula milk resumed. At 28 days of age hematochezia and non-bilious emesis with abdominal distention were observed. Anatomic abnormalities such as malrotation and antral obstruction were ruled out by an upper gastrointestinal contrast study. FPIES was suspected when the symptoms persisted for another eleven days. Therefore, hydrolyzed formula was introduced, and the gastrointestinal symptoms ceased after six days (Fig. 1B).

3. Discussion

The relationship between gastrointestinal system and heart disease has gained attention over the last years, particularly the independent role of intestinal flora and the dysregulation of its homeostasis in the context of worsening heart failure [10,11]. Reduced intestinal perfusion due to inadequate cardiac output can cause dysfunction and structural alterations of the intestinal mucosa and bowel wall. The damage induced by the ischemia-reperfusion injury and the subsequent inflammation due to the activation of inflammatory cytokines, compromises the intestinal barrier function and increases permeability, leading to bacterial translocation, which alters the intestinal flora [11]. The hypothesis of pathogenesis that leads to FPIES or FPIAP resembles this mechanism. Contact to a food allergen causes a T-cell-mediated response and release of proinflammatory cytokines (mainly TNF-alpha), that cause local inflammation and increased intestinal permeability. The subsequent influx of antigens and bacteria in the bowel wall alters the intestinal flora [12].

The immune system has an excessive reaction to a *dysbiotic* microbiota [9] and this abnormal response of the innate immune system to food-antigens is therefore enhanced by altered intestinal permeability [4]. In fact, a preserved intestinal microbiota is crucial for correct mucosal antigen sampling in the gut and protects from an inappropriate immunological reaction. This mechanism has been demonstrated in inflammatory bowel disease [7,11]. Moreover, the increased permeability of the intestinal wall reveals epitopes against which autoantibodies can be synthesized. In fact, leukocyte autoantibodies can be found in patients with non-IgE-GI-FAs [13]. In accordance to this, the histological findings of endoscopic biopsies in some patients with FPIES are similar to those found in patients with celiac disease [5,12].

Based on these assumptions, we hypothesize that patients with a partially impaired intestinal perfusion because of LVOT obstruction could have an increased risk for a FPIES or FPIAP due to the presence of an altered intestinal flora and a vulnerable intestinal wall. Our thesis of a locally dysregulated immune system is further supported by the specificity of the immunological response: the reaction is directed to specific antigens only, it is restricted to the gastrointestinal tract, has a delayed onset and is usually self-limiting. We think that the integrity of the intestinal wall plays a key role in the development of a locally competent immune system. Consequentially, when an adequate perfusion in patients with a LVOT obstruction is established (e.g. surgery), the intestinal wall recovers, the patient's immune system can regain its competence and shows a normal reaction to the food antigen.

In that regard, Myléus et al. demonstrated a connection between an altered intestinal flora and inflammation of the bowel wall, which can lead to increased risk for later celiac disease [14]. Lastly, FPIAP has been considered as a possible co-factor for patients with FTT in patients with CHD once before [15]. CM seems to be most common allergen in patients with CHD [16] and up to 30% of FPIES patients develop specific IgE antibodies against the incriminated food [5].

An increased incidence of NEC in patients with LVOT obstruction has been reported [1]. The clinical impact of FPIES and FPIAP and its similarities with NEC has been assessed in small cases series only [17,18]. In one report two of five patients had CHD [19]. Similar clinical and radiological presentation can lead to misinterpretation and to confusion in management of these high-risk patients, especially regarding the great differences in therapy and prognosis of the two diagnoses. Interestingly, our patients had isolated eosinophilia, normal white blood cell count and CRP, which in general is not consistent in patients with the diagnosis of NEC. The role of eosinophil blood count in order to different between NEC and FPIAP or FPIES has been evaluated before. Gordon et al. examined the eosinophil blood count in 3472 patients with the diagnosis of NEC [20]. They found 342 patients

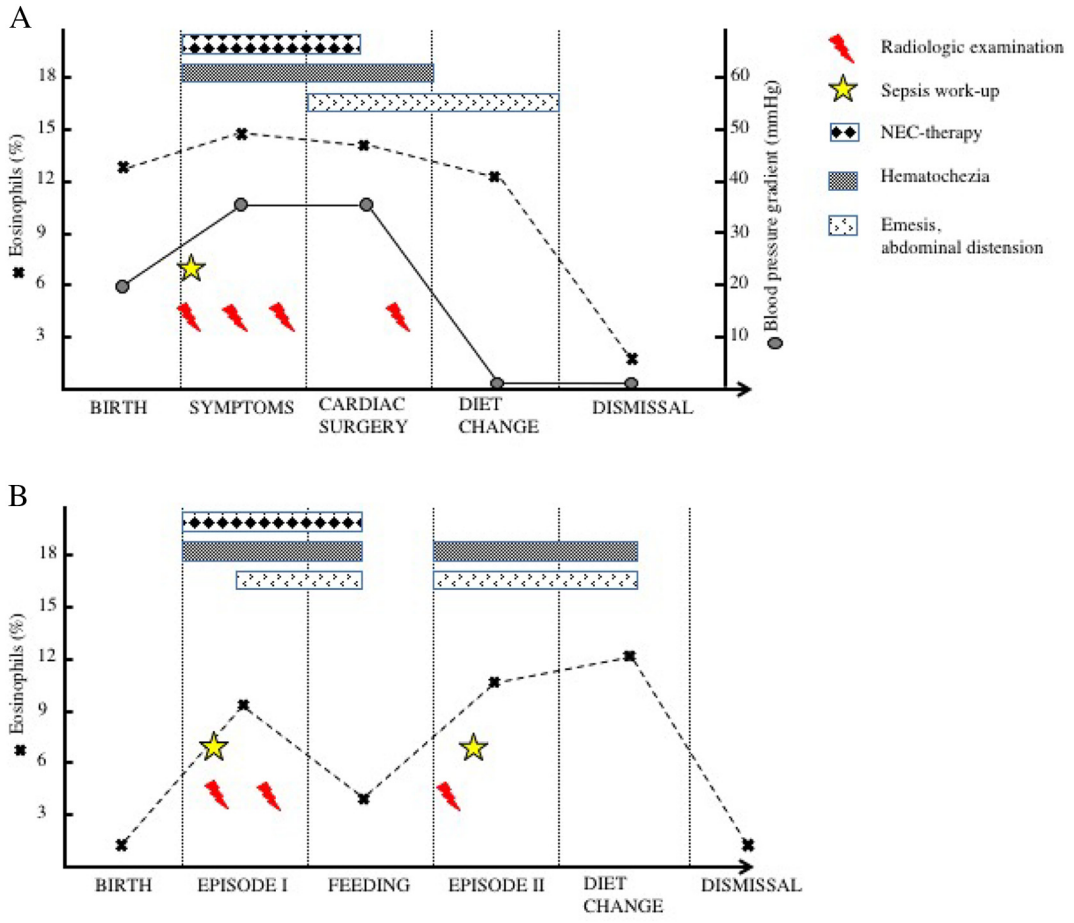

Fig. 1. A: clinical and laboratory course of case A.
B: clinical and laboratory course of case E.

in that cohort with isolated eosinophilia. Those patients showed a later onset of symptoms, that could be explained with an immunological reaction to the antigen. This patient group also had a lower mortality rate.

This concurs with our findings, that an elevated eosinophil blood count could help to distinguish NEC from FPIES.

4. Conclusion

A partially insufficient perfusion of the bowel wall in neonates with CHD and a LVOT obstruction could result in bowel wall damage which facilitates bacterial translocation. Thus leading to FPIAP or even FPIES triggered by an aberrant immune response to CM protein. In addition to improving the systemic perfusion, we propose a complementary or prophylactic strategy to protect the integrity and homeostasis of the intestinal flora. One angle could be to stimulate intestinal motility with prokinetic medication (erythromycin [21]) or to treat intestinal bacterial overgrowth.

Moreover, it can be argued, that the symptoms of FPIAP or FPIES should be addressed by the clinician as warning signs of intestinal damage with consecutive escalation of the therapy of cardiac failure by earlier surgical/interventional relief of the obstruction of the LVOT.

FPIAP or FPIES can manifest themselves with overlapping signs characterizing for NEC and need to be taken in account in well-appearing CHD neonates with LVOT obstructions presenting atypical NEC symptoms and signs. Hydrolyzed or amino acid-based formula milk as well as empiric elimination of possible antigens from the maternal diet should be preferred in patients with impaired intestinal perfusion. We are planning a more comprehensive retrospective analysis of our patients to corroborate our observations and hypothesis. The goal would be to prevent CHD neonates with LVOT obstructions from excessive diagnostic and therapeutic burden or overtreatment.

Author Contributions

Alessia Callegari: Design of the study, data collection/analysis, drafting/approval of article.

Sasha J. Tharakan: Interpretation of data, critical revision/approval of article.

Martin Christmann: Design of the study, interpretation of data, critical revision/approval of article.

Financial Disclosure

All authors have no financial relationships relevant to this article to disclose.

Conflict of Interest

All authors have no potential conflicts of interest to disclose.

Ethical Standards

All material in the manuscript has been acquired according to modern ethical standards.

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