

# Diseases of the Entero-Mammary Circle: A New Clinical Entity

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## ABSTRACT

**Background:** Gastrointestinal malabsorption of proteins from the diet of the mother can induce diseases in breast fed infants. The malfunction of the gastrointestinal tract (GI) of the mother is the basic process causing this disease. This new entity is under the scope of “diseases of the entero-mammary circle” (DEMC). Proteins different from homologues proteins of the breast milk, present in breast milk offered to the infant develops food allergy with clinical manifestation in different organs of the newborn and infant. Here we describe the most relevant clinical symptoms associated to this new entity the DEMC.

**Methods:** From January 2015 to January 2021, 100 charts from infants, age 0 to 6 months, were randomly selected from our clinic of Pediatric Gastroenterology and Food Allergy at Santa Casa da Misericórdia do Rio de Janeiro, Rio de Janeiro, Brazil. The inclusion criteria were: 1) To be exclusively breast fed since birth and 2) Diagnosis of food allergy through strict diet to the mother without cow's milk, egg, soy and wheat protein and subsequent oral challenge with ingestion of the seafood by the mothers and recurrence of gastrointestinal, respiratory or dermal symptoms by oral challenge positive. The exclusion criteria were the use of other any food besides the breast milk.

**Results:** The onset of symptoms in the patients studied starts early in life. In the GI system the prevalent clinical symptoms were blood in stool, gastro-esophageal reflux, abdominal distention, abdominal pain, diarrhea, constipation, bulky stools, flatus and vomiting, colic's and nauseas and hiccups. In the respiratory system of the patients, the clinical disturbance was snoring and rhinitis, sinusitis, excess of mucus, chronic cough, and asthma. In the skin system, was prevalent the pallor, atopic eczema, eczema of folds, erythema of the cheeks, per oral erythema and seborrheic dermatitis. Related to the central nervous system we found sleep disorder, insomnia, irritability, and lethargy.

**Conclusion:** The present study was developed to explore the broad spectrum of the DEMC, presented as different clinical pictures in infants, exclusively breast fed, compromising all systems such the GI tract, the skin, the respiratory system, and the central nervous system.

**Keywords:** Breast milk colitis, BMC and food allergy, constipation and DEMC, diseases of the entero-mammary circle (DEMC), DEMC and food allergy.

**Submitted :** January 11, 2022

**Published :** June 2, 2023

**ISSN:** 2593-8339

**DOI:** 10.24018/ejmed.2023.5.3.1205

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## I. INTRODUCTION

Breast milk is the gold standard of feeding for babies and exclusive breast feeding is recommended by the World Health Organization (WHO) for up to 6 months. The possibility of gastrointestinal symptoms with breast milk is much lower than with cow's milk-based formulas, however, they exist and it is very difficult to assess whether they are pathological or functional conditions. The functional digestive pictures in infants have specific definitions [1] where babies with exclusive breast feeding are not excluded. It is necessary to objectively define whether an exclusively breast fed infant has gastrointestinal symptoms due to a

functional or pathological condition. The pathological pictures can include infectious or metabolic possibilities and it is part of the discard in charge of the pediatrician. However, the possibility of a food allergy due to foods that the mother consumes, especially cow's milk protein, is the most frequent condition in pathological gastrointestinal conditions in babies, especially allergic proctocolitis [2].

Unlike functional symptoms, food allergy is a systemic condition, with variable symptoms of the digestive system but also dermal, respiratory and neurological symptoms. Symptom pleomorphism makes assessment difficult, requires clinical acuity and experience.

The correct diagnosis of food allergy in these children is mandatory in these cases. The history is an important starting

point, and recently we developed a clinical diagnosis based in anamnesis as the basic tool for the diagnosis of food allergy [3]. Another interesting approach to the clinical diagnosis was developed by the European Academy of Allergy and Clinical Immunology, based on the symptoms, the suspected foods and dietary intake, the basic tools to the diagnosis, divided into stages using traffic light labeling (red, amber, and green). These tools will provide a practical approach to support food allergy diagnosis. Unfortunately, both tools were not yet validated in diverse age groups, disease entities and in different countries [3], [4]. There is a third score for the diagnosis of allergy to cow's milk protein that has been validated in several centers [5], however, its approach based on these verity of the symptoms is opposite to our position of the timely and early diagnosis and does not make it applicable for this condition (DEMC) that we are postulating, where the subtlety of the symptoms is the rule and not the exception.

Any error in overestimating food allergy in these children can lead to dietary errors in mothers or interruption of breast feeding, while underestimating it can have negative consequences in babies, with progression of inflammation not only gastrointestinal but also systemic [6].

Considering the diagnostic difficulties of food allergy in patients with exclusive breast feeding and the vital importance of detecting it, to give an appropriate management and to avoid the unnecessary withdrawal of breastmilk, we present a new diagnostic entity: entero mamarium circle disease.

We described this entity for the first time in an abstract presented at the 3rd World International Scientific Conference (WISC 2014). We studied from January 2009 to January 2011, charts of 24 children, age 0 to 6 months, diagnosed with breast milk enteropathy. All children were exclusively breastfed since birth. DEMC is one of the most relevant syndromes present early in life, misinterpreted in origin, characterized by clinical manifestations associated to food allergy, related to the gastrointestinal tract, to the respiratory system, to the skin and to the central nervous system [7].

The present study was developed to explore the broad expectrum of the clinical picture of children presenting symptoms exclusively breastfed.

## II. MATERIAL AND METHODS

### A. Patients

One hundred children between the ages of zero and six months, attended consecutively at our clinic of Pediatric Gastroenterology and Food Allergy (Rio de Janeiro, Brazil) in the period from January 2015 to January 2021 were enrolled in this study. The inclusion criteria were: 1) To be exclusively breast fed since birth and 2) Diagnosis of food allergy through strict diet to the mother without protein from cow's milk, egg, soy and wheat and subsequent oral challenge with intake of these foods by the mothers and recurrence of symptoms (gastrointestinal, respiratory or dermal with an oral challenge positive). The exclusion criteria were the use of other any food besides the breast milk. All medical records of the infants were analyzed carefully regards anamnesis, clinical manifestation, and clinical diagnosis.

We collect information by reviewing the medical records, characterizing this study as a retrospective cross-sectional study.

The Ethics and Research Committee approved this research project under number CAAE 66813917.0.0000.5283. The Free and Informed Consent Term is in accordance with resolution number 466 of December 12, 2012, of National Health Council, on research involving human beings.

## III. RESULTS

Among the 100 infants studied, age 0 to 6 months, diagnosed with DEMC, the onset of symptoms starts in the first month of their lives in 48 of the patients, in 21 of the patients in the second month and in 31 patients the symptoms appeared between the 3rd to the 6th months of life and, as a rule, a mixture of symptoms of different systems were present in all patients.

In the GI system blood in stool was the most common form of presentation of this disease presented in 58 patients. Gastro-esophageal reflux was present in 41 of the patients; abdominal pain in 33; diarrhea in 20 patients; constipation in 16 patients; bulky stools, flatus and vomiting present in 12 of each one of the patients; colic's and nauseas in 10 of each one of the patients; and hiccups in 4 patients.

In the respiratory system (RS), snoring and rhinitis was present in 17 of each one of the patients; sinusitis, and excess of mucus in 9 of each one of the patients; and asthma and chronic cough in 5 of each one of the patients.

In the SALT system, pallor was present in 42 of the patients; the skin shown atopic eczema with a presence in 17 of the patients; followed by eczema of folds in 13 patients; and erythema of the cheeks, perioral erythema, and seborrheic dermatitis in 8 of each one of the patients.

Related to the CNSALT system we find sleep disorder in 19 of the patients; irritability in 12 patients; and insomnia, and lethargy in 4 of each one of the patients.

In the genetic background the family history of allergy shows rhinitis present in both parents, with a prevalence in 37.4% of the father and 8,3% in the mother and intolerance to food in 16.6% of the mothers and 8,3% of the fathers. Asthma was present in 25% of the mothers and in 20,4% of the fathers [8].

## IV. DISCUSSION

In our study all systems were affected with prevalence in the GI system. The BMC was the prevalent disease among all the GI diseases, present in 58 patients. Rhinitis was the prevalent disease among all RS diseases, present in 17 patients. Pallor was the prevalent disease among all S diseases, present in 42 patients. Sleep disorders was the prevalent disease among all CNS diseases, present in 19 patients. BMC is the principal cause of allergic colitis with blood in stools early in life in the scope of DEMC. Colitis is a multifactorial inflammatory reaction causing microscopic lesions in the large intestine not necessarily related to macroscopic alterations and may be diagnosed in several age

groups, and when manifested in the early childhood, food allergy is one of its main features [2], [7], [8].

The mother tends to be frightened when noticing blood in the stool when exclusively nursing her newborn child [7], [8]. The disease may occur by proteins ingested by the nursing mother on her diet, mainly in connection with cow's milk protein or soy protein. Other proteins could be involved in the disease. Those mothers have DEMC, and the protein of their diet goes to the breast milk and was the main causative agent of breast-protein induced allergic colitis [6], [9], [10].

The diagnosis of allergic colitis could be reinforced by the histological finding of increased infiltration of eosinophils in the rectal mucosa. These finding, associated with data from the anamnesis and to the clinical multisystemic involvement, are definitive elements in the diagnosis of allergic colitis in patients with DEMC. A non-invasive color doppler ultrasound could be done in DEMC to reinforce the clinical diagnosis [9]-[11].

Reflux, abdominal pain, constipation, and diarrheas are also prevalent, indicating an alteration in peristalsis secondary to the relapse in the motor activity of the enteric nervous system, generating gastroparesis (reflux and dyspepsia), enteroparesis (abdominal distention and abdominal pain) or colon paresis (constipation or diarrhea) [12]. In the respiratory system the prevalent symptoms were secondary to secretion in the upper or in the lower respiratory tract. Snoring and rhinitis, sinusitis and excess of mucus and asthma and chronic cough were the prevalent symptoms. In the SALT system the prevalent symptoms were secondary to inflammation in the skin, resulting in pallor, atopic eczema, eczema of folds and erythema of the cheeks, perioral erythema and seborrheic dermatitis. The symptoms related to the CNSALT system, secondary to inflammation in the neurons, were sleep disorder, insomnia, irritability, and lethargy [7], [8].

These symptoms can be confused with colic, restlessness, as parents may often initiate home-based measures to restrain the problem, with no positive results, which may further increase their distress upon the discomfort the child is experiencing, what indicated that some cases may sometimes be treated inappropriately, or even be unnoticed to parents and general population. Therefore, it is important to have adequate knowledge for proper treatment, diminishing infant and parenting uneasiness. The infant could be healthy, although the symptoms may be very intense. They can cry a lot, struggling with mother's breast and bending over their backs during breastfeeding. This picture causes great distress in the parents, especially for the nursing mother. The clinical spectrum ranges from IgE mediated reactions, presenting with urticaria or angioedema, vomiting or diarrhea, asthma, and convulsion, to intermediate and late-onset reactions, including atopic dermatitis, infantile colic, gastro-esophageal reflux, esophagitis, infantile proctocolitis, food-associated enterocolitis and constipation. Affecting all systems, the DEMC has a large clinical spectrum [13].

In summary, the clinical spectrum, systems affected and the most frequent related diseases in DEMEC are: *i)* GI: BMC, Reflux, Constipation, Diarrhea, Abdominal Distention and Colic's, *ii)* RS: Snoring, Rhinitis, Sinusitis, Mucus, Chronic cough, and Asthma, *iii)* Skin: Pallor, Urticaria,

Eczema, Erythema and Seborrheic Dermatitis, *iv)* CNS: Sleep Disorders, Irritability, Insomnia, and Lethargy [3], [13].

Breast milk is produced by the mammary gland under the influence of the enteromammary circle of the mother. The bipolar extreme of this circle is represented in one extreme by the GI tract of the mother, with their GALT system, and in the other extreme is represented by the mammary gland. Any protein presented in the diet of mothers suffering of GI diseases can go to the breast milk and induce disease in the breastfed baby, causing the DEMC [9]. The DCEM can follow two modalities of maternal antigen (Ag) transmission: one in intrauterine life: children are born sick, having received Ag aggressors via the uterine route and the other after birth: children who shown symptoms after birth receiving Ag via breast milk [9].

DCEM can be caused by an antigen from several proteins being the cow's milk the most frequent. Because of absorption of those proteins from the mother's milk, once they are in the intestinal lumen, they can reach the terminal ileum and be absorbed by the M Cell of the intestinal mucosa. Immediately the dendritic cell (DC) will present this new protein to the T CD4 lymphocytes starting an immune reaction resulting in food allergy. Inflammatory changes in the intestinal mucosa resulting from the immune reaction induced by the food allergy can be found in the entire gastrointestinal tract. In infants under 6 months of age, however, they are more commonly identified in the colon and in the rectum [7].

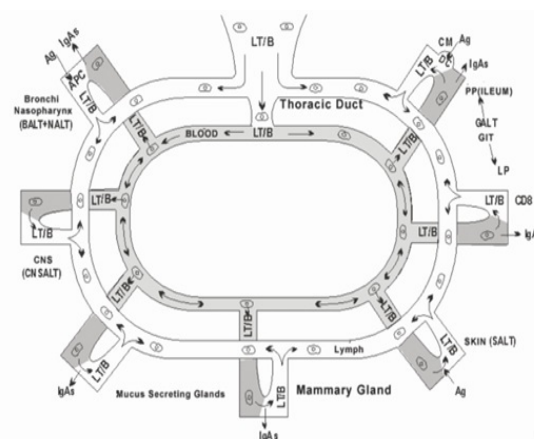


Fig. 1. Interaction of the lymphatic system and blood with the connected mucosal associated lymphoid tissues of the MALT systems. GALT: gastrointestinal associated lymphoid tissue; BALT: bronchial associated lymphoid tissue; NALT: nasopharyngeal associated lymphoid tissue; SALT: skin associated lymphoid tissue; CNSALT: central nervous system associated lymphoid tissue; GIT: gastrointestinal tract; LP: lamina propria; PP: Peyer's patches in the Ileum; LT/B lymphocytes T and B; MC: M cell; DC: dendritic cell; Ag: antigen; APC: antigen presenting cell; IgAs: secretory IgA immunoglobulin; Thoracic Duct; Mucus Secreting Glands and Mammary Gland.

Unexpected and occasional exposure to cow's milk proteins can initiate the sensitization process in predisposed children; Subsequent exposure to minimal amounts of bovine proteins, present in breast milk, can serve as an allergy trigger [14].

The main clinical manifestations of DCEM are regurgitation and vomiting, colic, diarrhea with or without blood, presence of blood in non-diarrheal stools and intestinal constipation. The disease is more common in the first months of life; however, it may appear later. The duration of the



DEMC did not induce worsening of the infant's nutritional status [15].

Apart from IgE-mediated atopic manifestations, T cell-mediated reactions have been demonstrated in infants with DEMC. The clinical spectrum ranges from immediate-type reactions to intermediate and late-onset reactions [7], [8], [14].

In previous studies we found false information regards DEMC in considered exclusively breastfed babies. In one survey 85 of our children supposed to have DEMC, had exposure to cow's milk in the first 48 hours of life. In other study we found that nine patients who were breastfed developed a reaction to cow's milk proteins, while considered being fed maternal milk exclusive. With a careful look in the medical records, we got the information that all had received cow's milk during the first 3 days of life in the nursery. Based in this data we stress all pediatricians to carefully ask direct question regards the use of formulas in the first days of life. In those cases, we must assume that the disease could be developed by the cow's milk and not by the breast milk in breastfed baby [7], [8], [15].

We must consider to ruled out the diagnosis of food protein-induced enterocolitis (FPIES) since this disease could be present in the first 6 month of life. This entity is a non-IgE-mediated gastrointestinal food hypersensitivity, mediated by cells. Differs from DEMC by the induction of malabsorption and poor gain of weight. The prevalence of FPIES is low. Most patients recover in early childhood [14], [16].

Eosinophilic or allergic colitis in formula fed babies, with increased colonic mucosal eosinophils, in biopsies of the rectum, is related to cow's milk formulas. Its exact prevalence is unknown. In Brazil, it was found that 20.6% of infants with allergy to milk with bleeding in the stool, had eosinophilic or allergic colitis. In American children we do not have data in isolated increased colonic mucosal eosinophils [17]-[19].

DEMC is a condition commonly managed by general practitioners and pediatricians. The treatment of DEMC relies on maternal elimination diets. The principle of the treatment of patients with food allergy is allergen avoidance and hypoallergenic formulae [20].

In a situation of decision make we must consider tree fundamental things: the lower cost of breastfeeding compared to the use of hypoallergenic formulas; the unique link promoted by mother-child by breastfeeding; and the beneficial role of breastfeeding in the nutritional status of the baby [6], [8].

## V. CONCLUSION

The present study was developed to explore the broad expectrum of the clinical picture of children, exclusively breast fed, presenting diseases associated to the malfunction of the entero-mammary circle (DEMC). We consider this disease the first manifestation of food allergy occurring in newborns and in infants, in the first six months of life. The findings of the compromised clinical expectrum are present in all systems such the GI tract, the skin, the respiratory system, and the central nervous system.

## ACKNOWLEDGMENT

We kindly thank all the patients who took part in this study.

## CONFLICT OF INTEREST

Authors declare that they do not have any conflict of interest.

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