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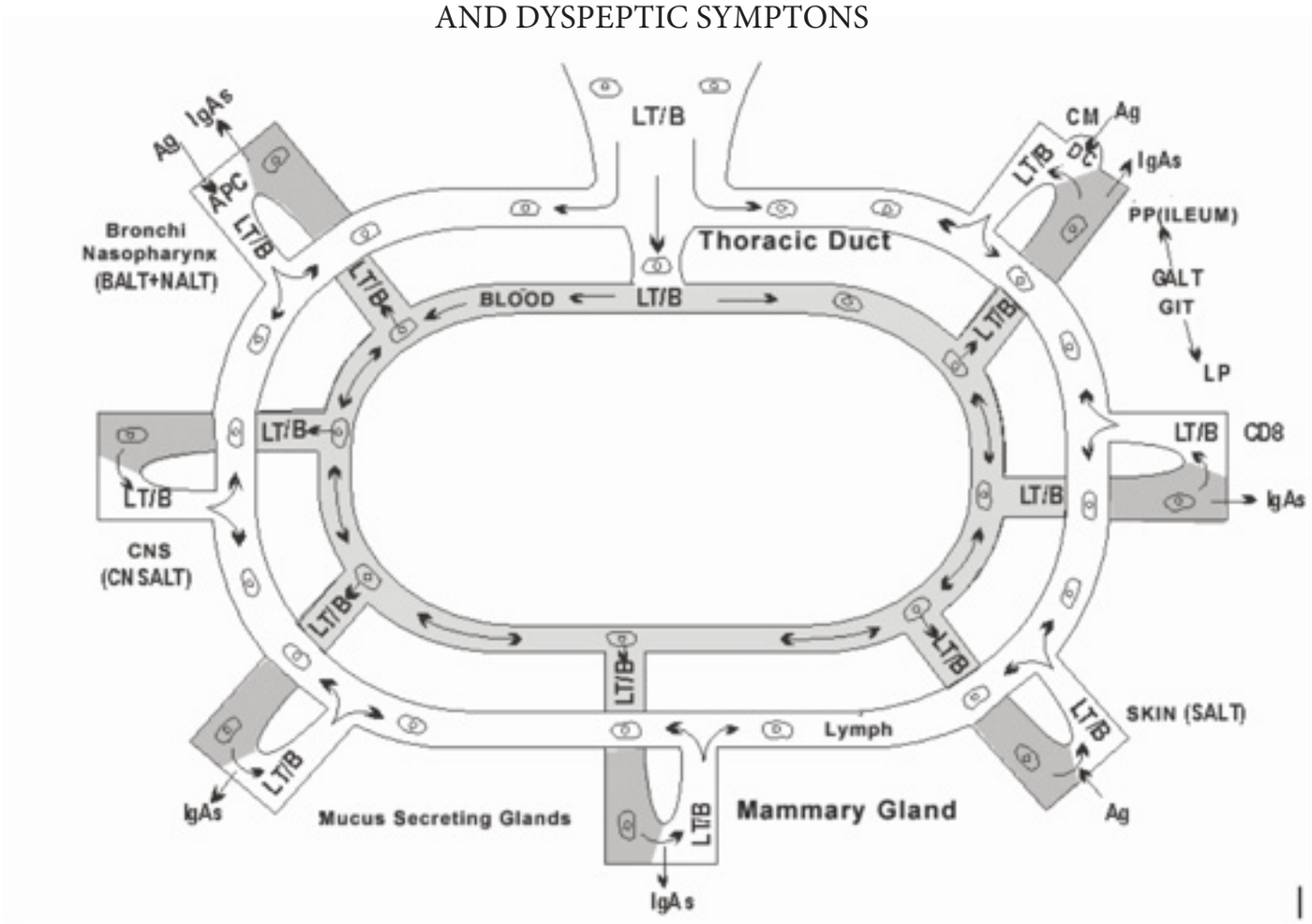
COW´S MILK ENTHEROPATHY

REPORT OF A NEW IMMUNOLOGICAL MEDIATION IN FOOD ALLERGY: CHILDREN WITH SEVERE FOOD ALLERGY MEDIATED BY A VERY LOW SUBSET OF CD8 RESULTING IN A HIGH RATIO CD4/CD8 T CELL

DISEASES INDUCED BY MALFUCTION OF THE MOTHER ENTHEROMAMMARY CIRCLE

DELAYED GASTRIC EMPTYING (DGE), GASTROESOPHAGEAL REFLUX (GER) AND DYSPEPTIC SYMPTONS



EDITORIAL

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CONTEÚDO

COMENTÁRIO DO EDITOR

Neste quarto volume de Journal of Food Allergy, versículo 3, quatro artigos originais sobre temas importantes da clínica diária, relacionada com as queixas sobre alergia alimentar são apresentados a nossos leitores, todos eles do grupo de especialistas em alergia alimentar dirigidos pelo Professor Aderbal Sabra.

No primeiro artigo deste número é relatada a associação entre alergia alimentar e a ocorrência da mediação imune por deficiência dos linfócitos CD8. Este trabalho foi apresentado no Congresso Mundial das sociedades de gastropediatria, nutrição e hepatologia, que ocorreu em Paris, tendo merecido a maior pontuação dentre todos os temas livres, lá apresentados, neste tópico sobre alergia alimentar, pois relata um novo tipo de mediação imune até então desconhecido para a alergia alimentar.

O segundo artigo aborda a causa mais frequente de Alergia Alimentar em todo o mundo, a Enteropatia do Leite de Vaca, com a experiência do grupo do Rio de Janeiro.

O terceiro artigo é revestido de grande expectativa pois relata um tema pouco conhecido na Alergia Alimentar, a "Doença do Ciclo Enteromamário", uma situação frustrante para as mães que amamentam com exclusividade seus filhos, pois a doença vem da própria amamentação. Nesta circunstância a doença ocorre por aumento da permeabilidade do trato digestivo das mães e absorção de macromoléculas proteicas de sua dieta, que vão causar a sensibilização dos seus amamentados, resultando daí entre outras doenças a conhecida "Colite do Leite Materno".

O quarto artigo do grupo trata de um dos temas pioneiros nas suas publicações: o estudo dos distúrbios motores que decorrem da alergia alimentar. Todo paciente com alergia alimentar tem como consequência, um distúrbio motor que vai originar, no segmento intestinal comprometido, dependendo de sua idade, diferentes manifestações clínicas a saber: refluxo no lactente jovem ou dispepsia no escolar, adolescente e adultos ou a distensão abdominal e a constipação em qualquer idade.

Aderbal Sabra, MD, PhD
Editor-Chefe
Journal of Food Allergy

Original Article

COW´S MILK ENTHEROPATHY

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INTRODUCTION

Food allergy is "an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food protein". The cow milk protein (CMP) is the first food protein ingested by children after the mother breast milk. Cow's milk protein allergy (CMPA) is the most frequent food allergy in the first months of life1. CMPA, which is also commonly referred to as cow's milk allergy (CMA), or cow's milk enteropathy (CME) is the leading cause of food allergy in infants and children younger than three years of age2.
Comparable international epidemiological evidence on CMA prevalence is lacking, predominantly due to methodological and geographical differences in clinical evaluation 3. European prospective cohort studies from the last 15 years suggest that the prevalence of CMA is between 1.9% and 4.9%; this is consistent with a 2002 meta analysis of 229 articles on CMA which found that CMA is the most common food allergy in early childhood with an incidence of 2% to 3% in the first year of life 5 .
Food protein-induced enterocolitis syndrome (FPIES), named by american authors is now the usualy nomination to CMA. Is a non-IgE-mediated gastrointestinal food allergic disorder 5 . Diagnosis is frequently delayed because of its nonspecific symptoms and absence of classic allergic mucocutaneous or respiratory symptoms (e.g., urticaria or asthma) and a lack of definitive diagnostic biomarkers.

- In general, the diagnosis of FPIES is based on clinical criteria 6,7 The tests that evaluate CMPA shall be requested for the patients with symptoms of suspicion of this disease. They will not be valid for studies in asymptomatic children (screening), for the positive value shows the sensitivity, not necessarily a disease.

- This however depends on definition of non-IgE-mediated allergy; while approximately 3-5%, a larger percentage of infants (10-15%) manifests gastrointestinal discomfort which sometimes could be classified as allergy.

OBJECTIVE

To study the main clinical manifestations and laboratory findings presented by patients with cow's milk allergy (CMA), or cow's milk enteropathy (CME).

MATERIAL AND METHODS

Medical records of 40 children and adolescents were studied, 21 males and 19 females with a mean age of 4, 2625 years (maximum: 12 years / Min: 2 months) with the diagnosis of food allergy and CME.

RESULTS

Chief Complain: 1 - weightloss (16-40%), 2 - abdominal pain (14-35%), 3 - diarrhea (13 - 32.5%), 4 – associated respiratory complains (12-30%), 5 - vomiting (7 - 17.5%). Other clinical Picture with less frequency: constipation and abdominal distension.
Malt systemn affected and Homing response: GALT - 40 (100%), BALT - 30 (75%), SALT - 28 (70%), CNSALT - 18 (45%)
Clinical main manifestations in each organ of shock: GALT: Diarrhea (19 to 47.5%), abdominal pain (15 - 37.5%), bulkystools (14-35%), lack of appetite (12-30%). Other less frequent: vomiting, reflux, bloating and abdominal distention. BALT: Rhinitis (11-36.66%), asthma / bronchitis (10 - 33.33%),

pharyngotonsillitis (9-30%), phlegm (9-30%). Other less frequent: otitis, sinusitis, snoring and coughing. SALT: Facial pale (18 - 64.29%), shiners (9 - 32.14%), prurigoestrófilo (8 - 28.57%), atopic eczema (6-21,42%). Other less frequent: urticaria and erythema-perianal. CNSALT: Irritability (9- 50%), sleepdisorder (7- 38.88%), Hyperactivity (4- 22.22%), headache (3-16.66%). Other less frequent: ADHD and fatigue.
LABORATORY tests: IgE: IgE increased: 20 (52.63%), the normal IgE: 18 (47.36%). (2 patients IgE Unknown); Ratio CD4 / CD8: CD4 / CD8 ratio was low in 16 cases (43.24%), CD4 / CD8 ratio was high in 10 cases (27.07%) and CD4 / CD8 ratio was Normal: 11 (29.72%). (3 patients with CD4 / CD8 ratio unknown) .IGG4 greater than IgG3: normal relationship: IgG3>IgG4 in 20 cases (60.6%); ratio reversed: IgG4>IgG3 in 13 cases 13 (39.4%) and 7 patientswith IgG3 and IgG4 Unknown.

DISCUSSION

Most infants with CMA develop symptoms within the first month after introduction of CMP-based formula. The majority has two or more symptoms from two or more organ systems. Prognosis of CMA in infancy is good with a remission rate of approximately 85% to 90% at 3 years. In particular, gastrointestinal symptoms show a good prognosis 8. While the majority of infants present with two or more symptoms, this may be an artifact of practitioners not identifying allergy in the presence of only a single symptom.
Cow's milk protein may cause food allergy, with quite variable clinical manifestation. By the time when the symptoms appear immediately, after some time or retarde, the food allergy reactions are characterized by a time relationship between the reaction and the previous exposure to the food. By the affected organ or system, for the allergy presents itself as syndromes. A prospective regular assessment for the potential cow milk sensitization by SPT and specific IgE may clarify the nature of the association and support the clinical surveillance.
Allergy to cow's milk is due to an immunologic response to milk protein with a Danish cohort study suggesting that 54% of milk allergies are IgE-mediated, and the remaining 46% are classified as non-IgE mediated 9.
This however depends on definition of non-IgE-mediated allergy; while approximately 3-5%, a larger percentage of infants (10-15%) manifests gastrointestinal discomfort which sometimes could be classified as allergy.
In Sommanus et al paper show clinicaly affected organ or systems involvements were skin (66.7%), gastrointestinal (GI) (44.4%) and respiratory system (66.7%). Eczema (37%) and maculopapula rashes (55.6%) were the most common manifestation of skin sensitization. Diarrhea (29.6%), vomiting (25.9%) and lower GI bleeding (22.2%) were the common GI manifestations. Hypersecretion (63%) and rhinitis (55.6%) were commonly found in those.(11)
The pathophysiology of FPIES remains poorly understood. It is generally thought that antigen specific T cells, possible humoral antibody-specific responses and proinflammatory cytokines that modify the permeability of the intestinal barrier are involved 11,12,13,14.
Immunoglobulin G (IgG) antibodies to food allergens are produced in both atopic and non-atopic children. Allergic symptoms and atopic sensitization are associated with high levels of specific IgG subclass antibodies to allergens, particularly IgG4. The production of IgE and IgG4 antibodies is regulated by similar mechanisms, e.g. IL-4 from Th2 cells induces both IgE and IgG4 switching in B-cells 15. In contrast, IL-10 inhibits IgE production but up-regulates the secretion of IgG4, suggesting different ways to control the IgE and IgG4 production16.

CONCLUSION

This study adds important clinical data to the understanding of COW'S MILK ENTEROPATHY. In our experience this clinical entity, occurs at any age, from infancy to adolescence and affect both sexes.

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Original Article

Report of a new immunological mediation in food allergy: children with severe food allergy mediated by a very low subset of CD8 resulting in a high ratio CD4/CD8 T cell

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INTRODUCTION

Food allergy (FA) to food proteins is characterized by an abnormal immunologic reactivity in certain genetically predisposed individuals. This response generates a wide variety of symptoms and clinical manifestations expressed in several affected organs systems, eg, skin, respiratory tract, gastrointestinal tract and in the central nervous system (1).
The gastrointestinal immune system, therefore, has the important obligatory dual function of selecting nutrients essential for cellular growth while simultaneously avoiding immunologic errors to food proteins (1).
The cellular participants of these interactions will determine whether these peptides of proteins will be recognized and processed with a resultant immune unresponsiveness referred to as immunologic tolerance (2).
Peripheral tolerance mechanisms protect the body from detrimental effects after activation of self-reactive T cells. Is now realized that active regulation by CD4+ and CD8+ T cells is one of the key mechanisms for the maintenance of self-tolerance and protection from autoimmune disease (3, 4, 5).
CD8+ T cells were previously viewed as so-called "Supressor T Cells" that counteracted the initiation of IgE-dependent allergic airway and skin reaction by suppressing allergen-specific IgE production and modulating the Th1/Th2 balance toward a Th1-dominant profile (6, 7).
In allergy mediated by IgE there is a relative deficiency of Th1 with a prominent Th2 response accounting for the excessive IgE production. If allergy is not mediated by IgE, the role of these extremely low CD8+ T cells has not been elucidated yet. Not one but Sabra et al reported that these very low CD8 T cells give worst prognosis for these patients, as a new mediator of food allergy in these patients (Sabra A. WCPGHN, Paris 2004).
In our Ambulatory Clinic of Food Allergy, we find that depletion of CD8+ T cells and high CD4/CD8 T cells ratio can be found in the absence of high IgE level in allergic patients, do this could have a role important and isolated of IgE type allergy in subset of allergic patients.
The present study is intended to characterize a group of patients carriers of a high CD4/CD8 T cell ratio, due to depletion of CD8 T cells, consulting to Ambulatory Clinic of Food Allergy. The goal is to explore the clinical bases of the phenomenon of depletion of CD8+ T Cells in food allergy children by contrasting with another group of food allergy children without depletion of CD8+ T cells.

METHODS

This is a retrospective exploratory study. Selected a group of patients of BSFA (Brazilian Society of Food Allergy) attended from 1999 to 2010. The selection was due to file numbering, seeking in sequential order.
"Case CD8 low" was defined as the patient present CD4/CD8 ratio greater than or equal to 4, which also had immunological assessment and prick test for food antigens. "Control CD8 normal" was defined as the patient present CD4/CD8 between 1.5 and 2.5, which also had immunological assessment and prick test for

food antigens. These controls were the one nearest to index cases, with this normal ratio CD4/CD8.
In both cases, we collected the corresponding history in a format designed. Subsequently, we did the data analysis in SPPS format (Portable IBM SPSS Statistics v19).

PATIENTS AND RESULTS

In a role of 600 patients searched we found 32 patients who meet the definition of case. This represents 5.3% of the total number of patients searched. Of these cases, 24 were children; we included these children and 19 control children nearest to these cases.
Children and girls are equally distributed. Age is different between cases CD8 low and controls CD8 normal, because the first are youngest. All infants of this report are cases CD8 low.
By anthropometry, almost all children are eutrophic. Except by 4 wasted and stunted children, all cases CD8 low. The physical exam showed very often pallor face, dermatitis and abdominal fussiness.(table1)
The chief complaints in both groups were gastrointestinal. Abdominal pain and constipation are frequent, but vomit and great stools were symptoms predominant in cases mainly. In controls CD8 normal respiratory complaint was more frequent than in cases CD8 low.(table 2)
By laboratory, almost all controls CD8 normal are IgE elevated (95%), whiles 2/3 of cases CD8 low are the same (16/24). In cases CD8 low, we find low gamma globulin and CD19 cells. Anemia is present in 20% of cases CD8 low and 5% of controls CD8 normal. Total protein was normal in all children.
Enteropathy in both groups was the main final diagnosis. But urticaria was present in a third of cases CD8 low and no one control. Asthma, rhinitis o gastrointestinal hypersensitivity are twice of prevalent in controls CD8 normal than cases CD8 low. (table 3 and 4)
In both groups, the antigens more prevalent by prick test were: Cow's milk, egg yolk, chicken, soja and bean.
By evolution of symptoms and nutritional management, 2/3 of cases CD8 low are intolerant to various formulas (soya, hydrolyzed, elemental) and were treated with rotation of foods. Only 3 controls CD8 normal (15%) have this finding in the evolution. (table 5)

DISCUSSION

Our clinic attends to heterogeneous group of patient with a main characteristic: food allergy. Then, is not surprisingly that cesarean delivery is very prevalent (about 90%) and genetics of atopy is too (80% of parents atopic). Cesarean section is more common in allergic individuals and correlated with increasing in three times more likely to develop food allergy (8), similar found by Sanchez-Valverde et al (9). The mechanism from this was postulated that as the cesarean delivered infant does not pass through the birth canal he or she is not inoculated with the bifidogenic microflora of mother vagina (10).
In this group of food allergic children, we show a subgroup very grave: The CD8 low group. We postulated that their worst evolution was due to impaired CD8 T cells regulatory function.
The predominance of infants is the first characteristic in this grave subgroup. Age is a major predisposing factor to cow milk protein allergy (CMPA). The reason that young children exclusively are affected is not known, but the inmaturity of the small intestinal mucosa may be a factor. Inmaturity is a key in an infant affected by food allergy but doesn't explain all this picture (11). Our result would be shown that if food allergy is grossly apparent very early in life the prognosis is the worst, about tolerance.
The regulatory function of CD8 T cells was explored by many authors. T lymphocites function to regulate the inmune response towars viruses, intracellular bacteria and parasites, whereas B lymphocites function to protect against bacterial organisms and produce inmunoglobulins. The microenvironment and macroenvironment of the gastrointestinal tract is continuosly exposed to bacteria, viruses and parasites but maintains a balance between active inmunity, tolerance and inmune suppression. Dysregulation of this controlled/physiologic inflammation in the gut can lead to mucosal injury and diseases such as inflammatory bowel disease (IBD), food allergy or celiac disease (1, 2, 12).
The regulatory function of CD8 T cells depends of interaction with other cells or mediators; these are part of immune adaptative response: The dentritic cells present pathogen associated antigens to T cells thereby activating the adaptative inmune response.

Activation and maturation of inmature dentritic cells is triggered by microbial pathogens. The interactions mediated by Toll like receptores results in maturation of dendritic cell, antigen presentation and release of cytokines, which determines the T-helper cell phenotype (either Th1 or Th2) (1, 13). Indeed, IFN-gamma and TNF-alfa have an important role in activating antigen-presenting cells and T cells and in the achievement of oral tolerance against food antigens. Atopic and cow's milk allergic infants have been shown to secrete reduced amounts of IFN-gamma and TNF-alfa (14).

Indirect evidence exists to suggest that the development of food allergy may be controlled by CD4+-CD25+ T reg cells. Mucosal induction of Treg cells in response to cow`s milk proteins or, alternatively, centrally generated Treg cells had become activated and expanded in children with outgrown food allergy (15).

CD8+ T-cells function as regulatory cells either directly by killing immune cells or indirectly by coopting other cells to produce suppressive molecules, such as TGF-β and IL-10. Emerging evidence suggests that regulatory types of B cells (Bregs) that are generated under inflammatory conditions are capable of inducing tolerance (16).

In an study, the total number of CD8+Tcells was significantly lower in infants with CMA when compared to healthy infants. In addition, the total number of CD4+ T cells was comparable between the two study groups, but the frequency of CD4+ T cells expressing TNF-alfa were comparable between the two study groups. All studies agree that the T helper 1-like cell count is low in atopic diseases. Because the defective IFN-gamma production seems to be a regulatory defect rather than an intrinsic genetic defect, a good candidate source of regulatory factors for the newborn is their mother's milk (14). Our cases CD8 low have a short course of breastfeeding (lower than 4 months).

The laboratory show predominance of a high IgE level in cases CD8 low, but we find 1/3 children without this characteristic. A low total IgE level does not rule out the diagnosis of CMA. It is unclear whether in CMA the milk-specific IgE antibodies contribute a considerable proportion of the total IgE level; however, regardless of this, a close correlation was observed between the total and milk-specific IgE values.

Inmunoglobulin G was normal, but a half of children CD8 low shown IgA values greater than normal. The number of IgA producing plasma cells is increased in children with cow's milk-induced enteropathy (17). Hypogammaglobulinemia was present in 2/3 of cases CD8 low too. This finding shows a persistent involvement of these mucosae can be accompanied by protein loss through faeces or through extensive cutaneous lesions, leading to hypogammaglobulinaemia (18). Interestingly, in a half of cases CD8 low, CD19 T cells are above normal values, showing an energic response to gammaglobulin leakage.

In infants transient hypogammaglobulinaemia has been linked to immaturity of the immune system associated with the mucosal barrier (low intestinal proteolytic activity, low acid secretion, immature microvillus membrane, absence of IgA and IgM from exocrine secretions, low concentration of IgA in intestine, reduced T helper type 1 lymphocyte function and diminished interferon-c production, etc (18).

In older children, despite the efficiency of this protein digestion, intact food antigens can be detected in the systemic circulation after a meal. The immune system is not ignorant of these dietary antigens, and food-specific antibodies in circulation are commonly found despite a state of clinical tolerance to the foods (19, 20).

One out six cases CD8 low shows IgM under normal values. The loss of IgM would reflect a severe intestinal involvement, because this protein has a high molecular weight (18).

All these laboratory anomalies were in absence of undernutrition or inmunodeficiencies. Only 4 patient (cases CD8 low) were stunted and wasted, due to chronicity of disease (all older than 1 year of age at consult date).

There are few studies about evolution of symptoms in food allergy children. Our group is mainly affected of gastrointestinal symptomatology. Grave enteropathy is evident by clinical findings as great stools, abdominal distenssion, pallor. Constipation is also clue for this diagnosis. In food allergy and enteropathy, these clinical findings are not only symptoms but clues for following. Our study explore persisting symptoms spite of adequate therapy. We show that is possible a loss of tolerance in previously tolerant children.

This finding have an postulated association: The CD8

low T cells. In this scenary, laboratory and clinical findings are clues for the recovery of food allergic children.

Recovery in food allergy is not the same that healing epithelia. It is known that and adverse reaction to food may trigger intestinal inflammation and provoke intestinal bleeding, particularly in babies, but appear clear that this may later induce chronic inflammation in the gut (20). Clinical recovery is a first signal, but, in absence of more information, laboratory findings in food allergy are important clues if a goal is a healthy adult.

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Annexes

Table N° 1.- Demographics and current history

Variable	Cases (n,%)	Controls (n,%)	Total (n,%)
Male	10(41.7)	11(57.9)	21(48.8)
Age (years)(mean,SD)	2.6(3.5)	3.1(2.5)	2.8(3.1)
Infant	7(29.2)	0	7(16.3)
Wasted	4(16.7)	0	4(93)
Stunted	4(16.7)	0	4(93)
Formula feeding at first day of life	14(57.9)	11(60.9)	25(59.5)
Exclusive breastfeeding first 4 months or more	10(41.7)	12(63.3)	22(51.2)
Allergy to soy formula	11(45.8)	5(26.3)	16(37.2)
Reason for query: Gastrointestinal symptoms	16(66.7)	11(57.9)	27(62.8)
Reason for query: Respiratory symptoms	4(16.7)	7(36.8)	11(36.8)
Reason for query: Skin symptoms	4(16.7)	1(5.3)	5(5.3)

*STANDARD DEVIATION (SD)

Table N° 2- Symptomatology by target organ

Symptomatology	Cases (n,%)	Controls (n,%)	Total (n,%)
SISTEMA GALT – GUT ASSOCIATED LYMPHOID TISSUE			
Great stools	13(54.2)	6(31.6)	19(44.2)
Diarrea	8(33.3)	5(26.3)	13(30.2)
Constipation	9(37.5)	7(36.8)	13(30.2)
Vomit	12(50)	5(26.3)	17(39.5)
Abdominal pain	13(54.2)	9(47.4)	22(51.2)
SISTEMA BALT – BRONCHIAL ASSOCIATED LYMPHOID TISSUE			
Cold	16(66.7)	10(52.6)	26(60.5)
Asma	5(20.8)	8(42.1)	13(30.2)
Rinitis	8(33.3)	3(15.8)	11(25.6)
Sinusitis	1(4.2)	5(26.3)	6(14)
SISTEMA SALT – SKIN ASSOCIATED LYMPHOID TISSUE			
Facial eczema	4(16.7)	4(21.1)	8(18.6)
Pallor	14(58.3)	4(21.1)	18(41.9)
Urticaria	4(16.7)	3(15.8)	7(16.3)
Bags eye's	5(20.8)	1(5.3)	6(14)

Table 3- Laboratory exams

Laboratory exams	Cases	Controls	Total
Hemoglobin(mg/dL)(mean,SD)	12.3(11.4)	12.3(9.8)	12.3(10.6)
Anemia (n,%)	5(20.8)	1(5.3)	6(14)
Eosinophils (mean,SD)	254.5(182)	399.5(687)	318.5(548)
Platelets (mean,SD)	358(101)	425.5(199.9)	387.5(548)
IgE UI/L (mean,SD)	110.2(62)	388(540)	233(399)
Anormal IgE (n,%)	16(66.7)	18(94.7)	34(79.1)
IgA mg/dL (mean,SD)	58.8(51.1)	63.7(47.7)	60.9(49.2)
IgM mg/dL (mean,SD)	82.7(52)	120(82)	98(68)
IgG mg/dL (mean,SD)	653(274)	844(315)	734(304)
IgG 1 mg/dL (mean,SD)	503(224)	811(663)	620(461)
IgG2 mg/dL (mean,SD)	128(115)	521(1341)	277(834)
IgG3mg/dL (mean,SD)	30(13)	71(87)	46(57)
IgG4 mg/dL (mean,SD)	22(25)	27(27)	25(26)
CD4% (n,%)	54.4(6.6)	46.2(8.4)	50.8(8.4)
CD8% (n,%)	23.8(6)	11.7(3.1)	17.1(7.6)
CD19% (n,%)	19.9(7.8)	28.9(43)	27.3(39)
CD 56% (n,%)	7.8(4.5)	5.3(4.5)	7.7(4.4)
Ratio CD4/CD8 (mean,SD)	5.05(1.02)	1.9(0.9)	3.67(1.7)

Table 4- Final diagnosis and resolution

Final diagnosis	Cases (n,%)	Controls (n,%)	Total (n,%)
Hypersensitivity GI	3(12.5)	4(21.1)	7(16.3)
Urticaria	7(29.2)	0	7(16.3)
Enteropathy	8(33.3)	5(26.3)	13(30.2)
Asthma	1(4.2)	2(10.5)	3(7)
Rhinitis	2(8)	2(10.5)	4(9.3)
Constipation	1(4.2)	5(26.3)	6(14)
Dyspepsia	2(8.3)	0	2(4.7)
Xerodermia	0	1(5.3)	1(2.3)

Table 5- Dietary management

Formula	Cases (n,%)	Controls (n,%)	Total (n,%)
Allergy to partial hydrolyzed	10(41.7)	1(5.3)	11(25.6)
Alllergy to extensive hydrolyzed	6(25)	4(21.1)	10(23.3)
Use of elemental formula	4(16.7)	2(10.5)	6(14)
Allergy to elemental formula	3(12.5)	0	3(7)
Intolerance to various formulas/use of "rodizio" of foods	16(66.7)	3(15.8)	19(44.2)

Original Article

Diseases induced by malfuction of the mother enthero-mammary circle

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INTRODUCTION

It is ancient wisdom that breast fed infant may react to food in their mothers' diets and In 1918 Talbot described for the first time a breast fed baby whose eczema was provoked by maternal ingestion of chocolate 1. Only relation between infantile colic and maternal ingestion of cow's milk has been the subject of controlled studies, two of the three studies being performed dobled bind 2,3,4. 34,35,36 Two studies found a positive association, and it was concluded that on third of breast fed babies with colic improved of their mothers excluded cow's milk from their diet.

Breast milk is produced by the mammary gland under the influence of the enteromammary circle of the mother (Fig 1) 5. The bipolar extremes of this circle is represented by the GALT system, in the GI tract of the mother. The other extreme is represented by the mammary gland. Any abnormality of the GI function of the mother, mainly those related the absorption of macromolecules from the GI tract, will impact their GALT system, with a generation of immunological responses that flow to the capillary stream of the lymphatic system, traveling from the GI tract to the thoracic canal. Through this canal the lymphocytes and cytokines, produced by the immunological response in the GALT system, will flow to the blood stream, until they reach the mammary gland and their target organ. In such circumstance, the baby will drink this milk, rich in antigens and antibody. This mother milk will induce different immunological and clinical responses in the newborn.

The mechanism could be that an allergic mother can transfer numerous factors through the placenta or breast milk and even through the transamniotic route. Examples include intact maternal IgE in amniotic fluid 6 , maternal DNA in cord blood7; leukocytes; chemokines, such as IL-8, RANTES, IFN-g–inducible protein, or monokine induced by IFN-g; allergens 8,9, and antibodies 1,6.

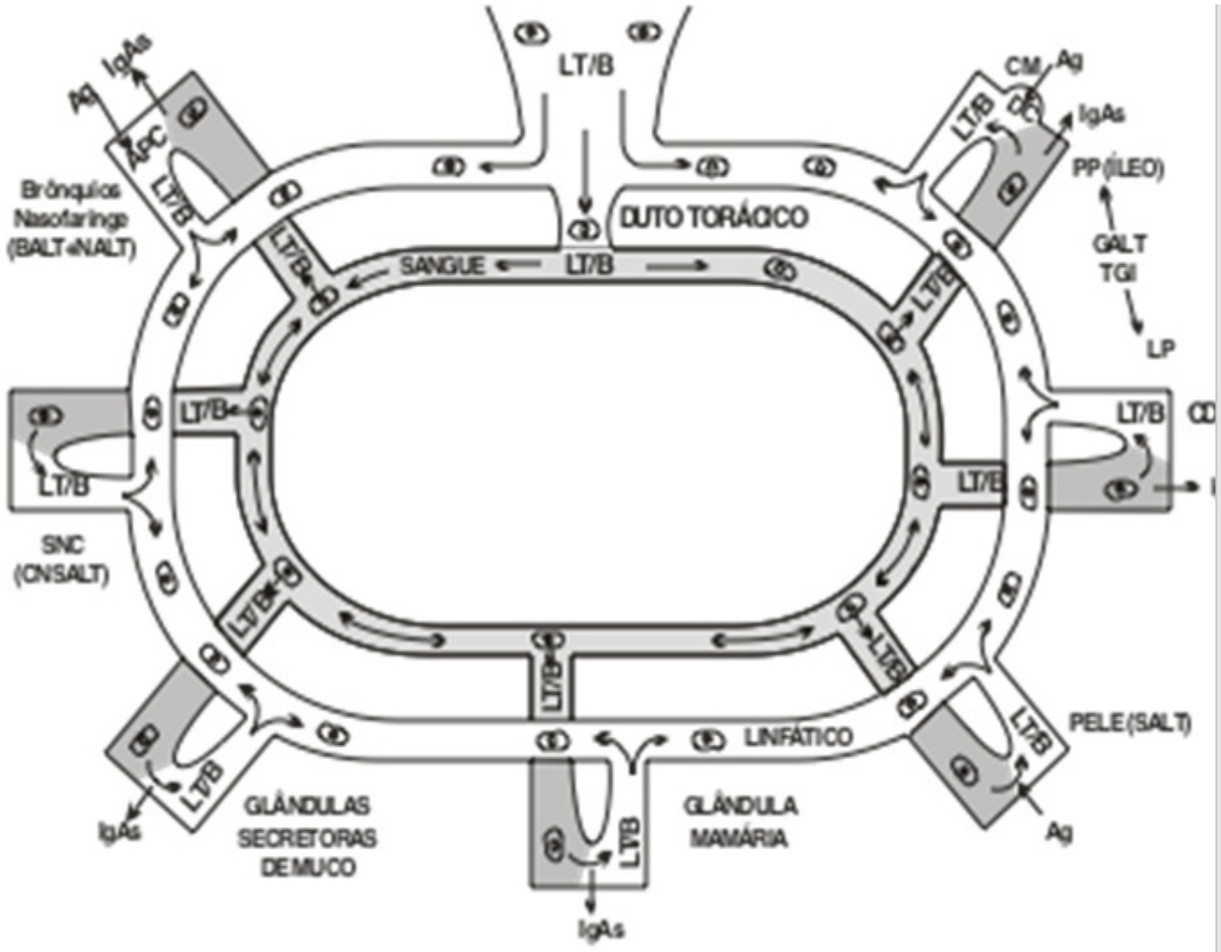

Fig 1: Sabra A, Interrelation among lymphatic and blood circulations, T cells responses and homing to target organs.

The classic picture of breast milk colitis show an apparently healthy children coming to the doctor in the laps of their mothers who have the chief complain that her child has bloody in stools. The rectal bleeding may present as bright red blood covering the stool or be streaks of blood mixed with mucous in stools. Physical examination of patients have a child apparently healthy and well nourished allowing us to rule out the possibility of serious diseases. Parents complain that the baby has colic and cry very easily. Some cases present with severe abdominal distension. Examination of the perianal rule out the possibility of fissures or perianal disease .

The human gut has little range of clinical manifestations before the attacks, and the more important are diarrhea and bleeding 10,11. The differential diagnosis of rectal bleeding in early life includes anal fissure, digested maternal blood, infectious enterocolitis and allergic colitis 10,12. This includes a broad spectrum of adverse reactions to food 10,13.

Infantile colitis can be caused by allergy to cow´s milk protein or other foods. Inflammatory changes of the intestinal mucosa seen in connection with food allergy may be found throughout the gastro-intestinal tract. But in infants less tha 6 mounths of age, they are most commonly found in rectum14 .

The symptons may desappear without any change in diet. In 50% of the children the symptoms disapear in the 1st year of life, and in almost all of them before 2

years of age15.
This clinical picture described above reflects the classic breast milk colitis, with the antigen in breast milk producing disease in the colon. In our experience, the expectrum of the gastrointestinal disease related to breast milk extends over the entere gastrointestinal tract, with children , exclusively in breast milk, presenting reflux, gastroparesia, small bowel enteropathy and also colitis.

OBJECTIVE

The objective of this paper is to show the broad spectrum of this disease related to the malfunction of the mother enteromamary circle.

MATERIALS

It´s a retrospective analyses of our data of gastroenterology clinic. The diagnoses of all are clinical and the symptoms are re-write in the specific note after that it is analyzed.
From January 2009 to January 2011, charts from 24 children, age 0 to 6 months, diagnosed with breast milk enteropathy where selected. All children where exclusively breast fed since birth.

RESULTS

The onset of symptoms starts in the first month of their lives in 48,3% of the patients, in 20.8% in the second month and in 33.2% the symptoms appeared between the 3 to 6 months of life.
The chief complains is blood in stool as the most common form of presentation of this disease. The symptomatology related to the GALT, was blood in stools present 58,3% of the patients. Gastro-oesofageal reflux, was the second most common GI complain, present in 41% of the patients, abdominal pain in 33.3%, diarrhea in 20.5% , constipation in16.6% , bulky stools, flatus and vomiting in 12.5%, colics and nauseas in 8,3% and hiccups in 4,1%.(table 2)
In the BALT system, the respiratory tract show snoring and rhinitis present in 16,6% of the patients, followed by sinusitis and excess of catarrh with 8,3% and asthma and chronic couth with 4,1%.
In the SALT system, the skin show as the most frequent alteration the atopic eczema with a prevalence of 16.6%, followed by eczema of folds in 12,5%, pallor, erythema of the cheeks, perioral erythema and seborrheic dermatitis where present in 8,3% of the cases. Related to the CNSALT system we find sleep disorder in 8.3% of the patients and insomnia, irritability and lethargy with incidence each one of 4.1
In the genetic background the family history of allergy show rhinitis present in both parents, in 37.4% of the father and 8,3% of the mother, intolerance to food in 16.6% of the mothers versus 8,3% of fathers. Asthma was present in 25% of the mothers versus 20,4% in the fathers.

DISCUSSION

The practice of breastfeeding has been rising in recents years, after declining in popularity for several decades 16.
The mother in your lofty mission of nursing is desperate when she sees her child passing, blood in stool, as is extremely disappointed when she know that their milk is responsible for the illness of his beloved son. The pediatrician must have many skills to convince the mother that she must follow breastfeeding her child while correcting her diet17.
The present study are developed to explore the broad expectrum of the clinical picture of children presenting symptoms exclusively breastfed . In our experience the gastro intestinal aspects of the disease range from esophagus to colon, also other clinical findings are present in various systems like skin, lungs and the central system, such picture presented in the broad spectrum of broad allergens.

Babies early in life produce a typical reflux like disease, usualy after birth.. A few months later they react with the typical breast milk colitis. In any circunstance a milk entheropaty is presented in all cases during the duration of the disease. In our data, blood in stools are the chief complain related to the disease of the entheromammary circle, presented in 58,3% of the patients. In literature, rectal bleeding was the main symptom that prompted the request for gastroenterological evaluation. In addition to bloody stools, watery (42%) or mucous stools (68%) were common 18. Vomiting, abdominal pain, diarrheas, constipation or skin complains are present in those babies. Excess of

cry and central nervous nervous system like alterations such as irritability and lethargy are also present.
Our data correlate well with to the literature regarding age of onset around 2 months of age 10 but can go with up to 6 months of life.
The most common gastrointestinal symptoms of breast milk entheropaty are blood stools17,12, but also in association gastro esophageal reflux (41%) and abdominal pain (33,5%).
Colicky abdominal pain in infants fed breast milk only has been shown to be related to the diet of mother 19,20. Proteins from the mother diets are excreted in breast milk 21, and serum antibodies against cow´s milk protein and eggs have been detected in exclusively nursed infants 22. The development of hypersensitivity to food antigens may not depend on the amount of antigens, but rather on the enhanced immune responsiveness of some infants to very small amounts of antigens 21. Small children with allergic proctocolitis usually recoverer very quickly after elimination of the allergens from diet 15. When the allergens is reintroducend, after 6 months to 1 year of the patient in the diet. There is rarely recurence 23.
Also riniths and snoring are not discribed in literature associated with breast milk.
Related to the central nervous system, sleep disorder are more frequent (8.3%) and in literature 17prickly are more comon.
Our data, related to skin show s atopic eczema in agreement with the data of Cant et al 20. Many studies shown the ability of atopy patch test in detecting delayed food reactions in infants with atopic dermatitis, with a high specificity and poor sensitivity in breast fed infants 24,25. Together with prick testing and serum specific IgE assay, a positive predictive value of about 95% can be attained 26.
The literature confirms 10,17 the importance of genetics in the back groud development of alergy.
Special consideration should be given to children born into both nonatopic or atopic families (ie, low-risk vs high-risk genetic background). In this context studies of epigenetics have to be forced to analyze connections of environmental and genetic modifications. Because studies have revealed that especially the genetic background and the homoeostasis of the TH1/TH2/ regulatory T-cell response of the mother can affect the child's immune response 27.

CONCLUSION

Their common clinical picture presented symptoms in the GI tract, ranging from the esophagus to the colon. Besides symptoms related to the GALT system, BALT,SALT, NALT and CNSALT where also compromised.
The diagnosis of breast milk enteropathy, should be established based on clinical history and should not be considered exclusively the data from intestinal bleeding. Clinical investigation must be to other organs, as in food allergy , to the respiratory tract, the skin, the central nervous system and deeply to the entire gastrointestinal tract.

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Original Article

DELAYED GASTRIC EMPTYING (DGE), GASTROESOPHAGEAL REFLUX (GER) AND DYSPEPTIC SYMPTONS

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INTRODUCTION

The prevalence of food allergic diseases in childhood is around 3%, with a range between 1.4-4% for common allergens (1,2)

In the recent years, gastric motility abnormalities have been cited as pathophysiological features of GER and functional dyspepsia that are closely related to dyspepsia symptoms. Gastroparesis is characterized by upper gastrointestinal symptoms secondary to delayed gastric emptying in the absence of mechanical obstruction

Gastro-oesophageal reflux (GER) is the passage of gastric contents into the oesophagus (with or without regurgitation and vomiting) lasting less than3minutes in the postprandial period with a few or no symptoms (3)

Functional dyspepsia as defined by the Rome III criteria refers to pain or discomfort in the upper abdomen associated with fullness, early satiety, bloating, belching, nausea, retching or vomiting (4).

In studies using "upper abdominal pain" as the definition,the prevalence of uninvestigated dyspepsia (UD) has varied between 7%-34.2 %(5,6,7,8,9,10).

Potential ethiopathogenic relationships between GER and CMA, the most common early childhood ailments, have been investigated for a few years now (5, 6,7).

In patients who were atopic with GER and functional dyspepsia, it has been suggested that allergic reactions to food proteins may be causative in the genesis of their symptoms (11).

Situations of reduced digestive capacity, like use of acid-suppression on treatment to DS and GER represents a threat to consumers of becoming sensitized to food proteins.Consequent clinical studies indicated the relevance of our findings for human patients. After 3 months of anti- ulcer therapy, 25% of anti-ulcer--treated patients revealed a boost in IgE formation towards a regular constituent of the daily diet, and 15% even showed IgE formation [11].

Scha SS et al demonstrates that allergen-induced changes in gastric myoelectrical activity are associated with degranulation of gastric antral lamina propria mast cells and association of released mast cell tryptase with proteinase-activated receptors on gastric mucosal nerve fibershave demonstrated IgE-mediated degranulation of mucosal mast cells that causes delayed gastric emptying through a decrease in both number and amplitude of gastric antral contractions (10,11).

Gastric scintigraphy with Tc99 has been considered the Gold Standard technique to measure gastric emptying time. This noninvasive technique allows direct image of gastrointestinal motility in real time under physiological conditions.

Objectives and Study

Gastroesophageal Reflux (GER) has a variety of etiologies including both anatomic and functional. Among the functional causes DGE appears to be the most important pathophysiological factor. Although some studies have suggested a relationship between GER and FA, there have been no studies linking FA with DGE

The purpose of the present study was the evaluation of the role of FA in infants with DGE and GER and in children, adolescents and adults with DGE and DS.

METHODS

Study Population: 24 infants and children (group 1), with chief complaint of GER, 58% male and 42% fema-

le, age ranging from 1 month to 36 month (average9.5 months); 22 children and adolescents (group 2) age 3-17 years with chief complaint of DS and 23 adults (group 3) with DS. We measured the delayed gastric empty by the "gold standard" Tc99 in all patients that entered in the study. FA and GER were diagnosed respectively by DBPCFC and 24 hours pH probe. DS was diagnosed by typical clinical picture and by upper GI endoscopy and biopsy. All subjects were Caucasian.

RESULTS

All subjects showed as they presented in our clinic, before treatment, with the maincomplaint of GER or DS, with abnormal variations in mean gastric emptying time (MGET) ranging from 75-250 min (x=100min). Following treatment with hypoallergenic diet, all subjects showed improvement in MGET ranging from 22-45 (x=35min). After challenge with milk all patients relapsed with the MGET ranging from 45-120 (x=75min).

DISCUSSION

In general, food can aggravate gastrointestinal symptoms by several mechanisms including: exaggerated physiologic responses of the gastrointestinal tract, food intolerance, allergy, increased intestinal gas, and modification of gut motility and sensation.

Allergy to protein from cow's milk or to other food products in children, irrespective of their age, is one of the more frequently recognized causes of secondary GER, although so far this relationship has been rarely described in clinical reports (16,17,18).Therefore, this is the reasonwe meet to describe this found.

Majority of population-based studies do not show any gender difference in dyspepsia prevalence. While few studies from different populations, have noted a consistent female preponderance with dyspepsia (19, 18, 20, 21, 22, 23, 24). What differs from our sample because there was a preponderance of males. We ascribe this; the samples are described in the literature for other diseases of adults-base, such as diabetes.

Regarding the gastrointestinal symptoms, dyspepsia but diarrhea or constipation showed a statistically significant association with milk protein IgG level. However, the association with milk protein IgG and dyspepsia was confounding as it was negative and not attributed to milk drinking or age.

Two studies by Cavataio and colleagues found significant improvement in symptoms in 30-40% of infants using an extensively hydrolysed formula, and concluded a high frequency of cow's milk protein allergy associated with GER (26, 27).In food-sensitive infantsand children, cow's milk has been shown thecause of gastric dysrhythmia and delayed gastric emptying which, in turn, may exacerbate GER and induce reflux vomiting (28). In a case series of patients with GER managed by clinical and histological examination of an oesophageal biopsy specimen, CMPA was confirmed at oral food challenge'(29) . Non- IgE-mediated CMPA was associated with more severe GER and 50% of challenges confirmed that patients had histological evidence of oesophagitis21. Facts that agree with our findings of improvement in all patients with feeding hypoallergenic, both DS as the GER, during this period.

CONCLUSION

The results of these studies suggest that FA was the origin of DGE in all cases. In infants and children, FA could be responsible for the elevation of MTGE in patients with GER and suggest that food allergy should be considered in the diagnostic work-up of all children with GER. The results also suggest that in children, adolescents and adults, with history DS, FA in these subjects could be responsible for the elevated MGET which in turn leads to DS as a consequence of DGE. All patients with symptoms of GER and DS, therefore, should be carefully examined to evaluate the pathogenic role of FA and to determine whether GER or DS is primary or secondary to FA and DGE.

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