GALACTOSEMIA, LACTOSE INTOLERANCE AND ALLERGY TO MILK PROTEIN: UNDERSTANDING OF PHATOPHYSIOLOGICAL MECHANISMS IN EARLY CHILDHOOD AND THEIR RESPECTIVE NUTRITIONAL PRESCRIPTIONS

GALACTOSEMIA, INTOLERÂNCIA À LACTOSE E ALERGIA À PROTEÍNA DO LEITE: COMPREENSÃO DOS MECANISMOS FISIOPATOLÓGICOS NA PRIMEIRA INFÂNCIA E SUAS RESPECTIVAS PRESCRIÇÕES NUTRICIONAIS

GALACTOSEMIA, INTOLERÂNCIA A LA LACTOSA Y ALERGIA A LA PROTEÍNA DE LA LECHE: COMPRENSÍON DE LOS CAMBIOS FISIOPATOLÓGICOS EN LA PRIMEIRA INFANCIA Y SUS RESPECTIVAS PRESCRIPCIONES NUTRICIONALES

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ABSTRACT: The objective of this study is to explain three similar pathologies that manifest in children in their early childhood, contributing to nutritionists and pediatricians and encouraging multidisciplinary work. The rare genetic error that affects neonates and prevents the metabolization of galactose is called classic Galactosemia. The body's immune response to children's early exposure to certain proteins, such as casein and lactoglobulin, is known as cow's milk protein allergy. Finally, lactose intolerance, which is subdivided into primary, secondary and congenital, which is the most common in children, making it impossible to produce the enzyme that would absorb lactose. This article will present a bibliographic review on the possible appropriate therapies to avoid nutritional deficiencies as a result of the need to restrict or exclude milk from their diets. The research used a total of 33 articles found in the Science, Scielo and Google Scholar databases.

KEYWORDS: Children. Milk. Deficiency. Pathology. Diet.

RESUMO: *O objetivo desse estudo é explicar três patologias próximas que manifestam-se em crianças na sua primeira infância, contribuindo com nutricionistas e pediatras e incentivando um trabalho multidisciplinar. O erro genético raro que acomete os neonatais e impossibilita a metabolização da galactose é denominado como Galactosemia clássica. A reação imunológica do corpo à exposição precoce das crianças a determinadas proteínas, como a caseína e lactoglobulina, é conhecida como Alergia à proteína do leite de vaca. E por fim, a Intolerância à lactose que é subdividida em primária, secundária e congênita, sendo esta a mais comum em crianças impossibilitando a produção da enzima que faria a absorção da lactose. Este artigo apresentará uma revisão bibliográfica sobre as possíveis terapêuticas adequadas para se evitar deficiências nutricionais em consequência da necessidade de*

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restrição ou exclusão do alimento leite nas suas dietas. A pesquisa utilizou um total de 33 artigos encontrados nas bases Science, Scielo e Google Acadêmico.

***PALAVRAS-CHAVE**: Crianças. Leite. Deficiência. Patologia. Dieta.*

***RESUMEN**: El objetivo de este estudio es explicar tres patologías cercanas que se manifiestan en los niños en su primera infancia, contribuyendo con nutricionistas y pediatras y fomentando el trabajo multidisciplinar. El raro error genético que afecta a los recién nacidos y que hace imposible el metabolismo de la galactosa se denomina galactosemia clásica. La reacción inmunológica del cuerpo a la exposición temprana de los niños a ciertas proteínas, como la caseína y la lactoglobulina, se conoce como Alergia a la proteína de la leche de vaca. Y por último, la intolerancia a la lactosa, que se subdivide en primaria, secundaria y congénita, es la más común en los niños, haciendo imposible la producción de la enzima que haría la absorción de la lactosa. Se presentará una revisión de la literatura sobre las posibles terapias apropiadas para evitar las deficiencias nutricionales como consecuencia de la necesidad de restringir o excluir los alimentos lácteos en sus dietas. La búsqueda utilizó un total de 33 artículos encontrados en las bases Science, Scielo y Google Academic.*

***PALABRAS CLAVE**: Ninõs. Leche. Deficiencia. Patología. Dieta.*

Introduction

The World Health Organization (WHO, 2000) indicates, until six months of age, the practice of exclusive and on demand breastfeeding, excluding the need for the inclusion of any other food sources, a recommendation adopted in Brazil. This becomes an important practice for the child's growth and development, providing beneficial nutritional repercussions for a lifetime. In addition, it significantly reduces the risk of morbidity and mortality, also affecting the psychic area of the infant and mother (OLIVEIRA, 2018; WHO, 2000; BRASIL, 2019).

Up to the sixth month exclusive breastfeeding is recommended, after this period complementary feeding begins, which will be of great importance to add to the infant's diet adequate foods that promote the necessary supply of nutrients and energy sources to the child and to avoid as much as possible the supply of ultra-processed, industrialized and excess condiments. In this phase, the infant will slowly become familiar with the food, being necessary to offer it eight to ten times, always counting on the exposure of a colorful and varied menu (DIAS; FREIRE; FRANSCESCHINE, 2010).

According to Pereira, Ferreira and Marques (2019), the inclusion of animal milk in the diet has an important biological role, favoring nutritional conditions, as a source of proteins,

vitamins and calcium and acting as a dietary supplement for the food supplementation of children (PEREIRA; FERREIRA; MARQUES, 2019). Despite scientific evidence pointing to beneficial results regarding lactation and the intake of milk of animal origin, there are cases of physiological changes that deprive and hinder infants of these incentives.

Galactosemia, for example, is a rare metabolic disorder that influences the appropriate metabolism of Beta-D-Galactose, comprising deficiencies that participate in the Leloir pathway, presented in the neonatal period, classified as Classical Galactosemia (GALT), Galactokinase Deficiency (GALK), UDP Galactose Epimerase Deficiency (GALE) and Galactosemia type IV (GALM) (WADA *et al.,* 2019; IWASAWA *et al.,* 2019).

Another possible pathology is Lactose Intolerance, classified as congenital, primary or secondary intolerance that occurs due to a deprivation in the enzyme β-galactosidase, which does not allow the hydrolysis of this disaccharide, causing the poor digestion of this carbohydrate (BRANCO *et al.,* 2018).

Finally, Allergy to Cow's Milk Protein, which is an immunological reaction caused by exposure to milk proteins and their derivatives (casein, lactoglobulin, lactoalbumin, serum albumin and immunoglobulins) (TĂTĂRANU *et al.,* 2016).

It is important to note that the number of children with food allergies and intolerances has increased, in addition health professionals (nutritionists and pediatricians) demonstrate errors in the concepts of the main therapeutic recommendations of these dietary changes and the necessary calcium intake for infants (CORTEZ *et al.,* 2007).

Therefore, the objective of this article is to explain the mechanisms of these pathologies, exposing their pathophysiology, symptoms, correct diagnosis, the deficit caused by the exclusion of breastfeeding and animal milk for infants and the most appropriate nutritional therapy for each case.

Methodology

For this study, a bibliographic review was carried out with the purpose of presenting subjects related to children and their eating disorders. For this, information was selected in other articles, found on the search sites SciELO, Science and Google Scholar.

The article included all publication dates, with preference for articles from the period 2016 to 2020, described in English, Portuguese and Spanish. The execution period started in September 2019 until March 2020, performed by two authors in electronic searches. In this search a total of 51 articles were found. Of these, 18 were excluded because they did not meet

the initial criteria (studies related to children), or because they did not meet the objective of the analysis in dealing with specific issues related to eating disorders described in the introduction.

Development

Classical Galactosemia (CG)

- Pathophysiology

Type I Galactosemia, which was mentioned at the beginning of the 20th century, is a pathology that presents a rare metabolic disorder of recessive and autosomal origin and can manifest more than 230 mutations to the gene that encodes the GALT enzyme (CAMELO JUNIOR *et al*., 2011), located on the short arm of chromosome 9, in band 13, divided between 11 exons. These modifications found are likely to cause anomalies, causing losses or decreased performance in the activities of the enzyme (SILVA; LOPES, 2015).

Individuals who have this profound deficiency are unable to perform the metabolic process of galactose-1-phosphate-uridyltransferase. In contrast, galactose-1-phosphate and galactose accumulate, being metabolized alternatively, forming galactitol and galactonate, which at high levels are toxic to the body and cause pathophysiological consequences (SILVA; LOPES, 2015).

In healthy children, galactose is converted to BD-Galactose to galactose-1-phosphate-uridyltransferase, accompanied by the action of the enzymes galactokinase (GALK), galactose-IP uridyltransferase (GALT) and UUD-galactose4-epimerase (GALE) part of the Leloir pathway, responsible for converting galactose to glucose-1P (GROSSIORD *et al*., 1998).

- Symptoms

Recurrent symptoms of Classical Galactosemia (CG) in children are vomiting, irritability, convulsions, unconsciousness (lethargy), enlarged liver (hepatomegaly), yellowish pigmentation on the skin or eyes due to the rupture of red blood cells (jaundice), low gain weight loss, difficulties in regaining birth weight, intellectual disability, enlarged spleen (splenomegaly), cirrhosis, nuclear cataract, abnormal amino acid levels in the urine (aminoaciduria), vitreous hemorrhage and the accumulation of fluid in the abdomen (ascites) (SWETHA; RAJESH, 2019)

- Nutritional Difficulties

The lactose present in breast milk, of animal origin and its derivatives is the main dietary source of galactose, therefore the insufficient intake of these food sources rich in proteins, calcium, riboflavin, vitamin D and fats may cause nutritional deficiencies in these infants and may trigger delays in growth due to poor bone formation, deficit of essential amino acids, developmental failures, difficulties in the healing and breathing process, as well as failures in the immune and hormonal systems (COMAN *et al.,* 2010).

- Nutritional Therapy

The treatment for the control of Galactosemia consists of removing from the diet of these children all foods containing galactose and lactose, replacing breast milk and animal origin with soy-based formulas and casein hydrolyzates (in this case, if the infant does not present liver problems) (MONROY SANTOYO, 2007). If necessary, insert the supplementation of calcium and vitamin D and K, and if the child is in the food introduction phase, complement with greeneries and vegetables of dark green colors that contain smaller amounts of galactose such as asparagus, kale, zucchini, cucumber, spinach, chard and lettuce and with fruits such as apricot, avocado, orange, mango, melon and grape (MEDIAVILLA DE PEDRO, 2018).

- Performance of Nutritionist\Pediatrician

The necessary method to arrive at a correct analysis of the disorder is to quantify the GALT enzymes present in this infant (GRAEF; WOLFSDORF; GREENES, 2010). The forms of diagnosis made by doctors are methods that are not included in the Brazilian neonatal screening (CAMELO JUNIOR *et al.,* 2011).

Therefore, the role of these professionals in the promotion and adequacy of health in galactosemic children is of great importance, therefore, it is necessary a complex therapeutic adaptation by the nutritionist due to the restrictions of calcium, vitamin K and D that the pathology causes, with the purpose of supply the daily recommendations of these micronutrients, dealing with few resources for infants (BERRY, 2017).

Lactose intolerance (LI)

- Pathophysiology

Lactose is an enzyme very present in human, animal and milk derivatives and its pathology is divided between Congenital, Primary and Secondary Lactose Intolerance (LI), the first being the most common in children (BRANCO *et al.,* 2018).

In the presence of Congenital IL, it is impossible to absorb carbohydrate due to the lack of production of the enzyme βgalactosidase (popularly known as Lactase), decreasing intestinal pH and causing gastrointestinal problems (MARCON; DIAS; BENINCÁ, 2018), consequently making it impossible the consumption of lactose in the diet.

Primary LI is characterized by a natural decrease in the production of lactase over the years, therefore, it is not very common in children and lactose does not need to come only from food. Finally, secondary LI is directly related to physiological problems in the individual's intestinal mucosa, which can be caused by prolonged use of antibiotics, Crohn's disease, gastroenteritis, diarrhea, duodenal ulcer, giardiasis and APLV, which alters the enzyme activity of lactase, being reversible if the gastrointestinal problem is treated and the epithelial cells return to the state's physiology (MARCON; DIAS; BENINCÁ, 2018; PEREIRA; FERREIRA; MARQUES, 2019).

- Symptoms

Gastrointestinal symptoms are abdominal pain, discomfort, flatulence, watery diarrhea, vomiting, constipation, bloating, dehydration and malnutrition (WALSH *et al.,* 2016).

- Nutritional Difficulties

Deficiency of mineral calcium and vitamin D can occur, which causes problems with bone weakness, skeletal malformation, difficulties in the development and satisfactory growth of children (ROCHA *et al*., 2012), as well as difficulties in the development of the immune system due to lactose malabsorption, which has a prebiotic function (HEINE *et al*., 2017).

- Nutritional Therapy

The prevention and reduction of problems caused by LI will depend on which of the three types of pathology the child has, therefore, the interventions may be to reduce or withdraw milk and its derivatives from the diet, ingestion of probiotics that will assist in the decomposition of carbohydrates and even the ingestion of exogenous lactase, which aims to reduce symptoms by hydrolyzing part of the lactose (MARCON; DIAS; BENINCÁ, 2018).

The milks indicated for intolerant infants are lactose-free formulas based on cow protein or formulas based on isolated proteins (ROCHA *et al*., 2012). Those responsible for children diagnosed with primary and secondary intolerance must control the amounts of lactose in their diets, since in most cases they have partial deficiency and are tolerant to foods that have lower concentrations of lactose (PERET FILHO, 2018). In the phase of food introduction, it is recommended to eat cheeses, yogurts, because in the fermentation process of these foods there is a pre-digestion of lactose, dark green vegetables and soft bone fish to supply their energy needs (ROCHA *et al.,* 2012).

- Performance of Nutritionist\Pediatrician

The diagnosis made by the pediatrician is based on the observation of the gastrointestinal symptoms presented by his patient after the consumption of dairy products and their derivatives, considering that primary intolerance is not common in children under five years old.

Laboratory methods can also be “hydrogen breath test with lactose”, “reduction of ph and H^2 in feces”, “genetic test for hypolactasia” and “duodenal biopsies” (HEINE *et al*., 2017).

After the medical diagnosis, the nutritionist will need to come up with functional therapy to adapt the child's diet, with the necessary calcium and vitamin D recommendations according to the presented intolerance.

Allergy to Milk Protein (AMP)

- Pathophysiology

AMP is a gastrointestinal disease that has an inflammatory reaction, since your immune system reacts when it comes into contact with cow's milk and whey proteins, the most frequent of which are casein, alpha-lactalbumin and betalactoglobulin. It is commonly

diagnosed in children up to three years of age and, today, its prevalence rate has grown, increasing its numbers by about 20% in a decade (MAIA, 2019).

The pathophysiology mediated by antibodies or/and cells can present four types of immunological reactions by Gell and Coombs: as (IgE-mediated), cytotoxic reaction, by immune complexes and cell-mediated, being the most common IgE-mediated reactions in infants and diagnosed more easily, as symptoms manifest quickly. Its occurrence is due to the early exposure of these infants to a diet (MAIA, 2019).

- Symptoms

Cutaneous manifestations may appear, such as dermatitis and urticaria, gastrointestinal, respiratory, systemic, cardiovascular and nervous problems, vomiting, constipation and anal fissures (MAIA, 2019).

- Nutritional Difficulties

The lack of cow's milk and its derivatives can lead to energy and bone problems due to the lack of calcium, proteins and vitamin D. Therefore, it is necessary that nutritionists and pediatricians monitor the development and growth of these children, adjusting until the case improves (PEREIRA; DA SILVA, 2008).

- Nutritional Therapy

In principle, treatment occurs with the total withdrawal of the intake of cow's milk and its derivatives from the infant and lactating diet (HEINE *et al*., 2017), replacing with extensively hydrolyzed formulas based on cow's milk protein. If this is not beneficial, it is recommended to use the base of free amino acids or even the re-lactation.

It is necessary to diagnose what the allergen is and exclude it, in order to offer the correct treatment that will bring benefits to this child, reducing the risks of nutritional deficits. During the food introduction phase, they will be able to consume food normally, only avoiding the consumption of two or more protein sources at a time, taking care with cross contamination (SOLÉ *et al.,* 2018).

- Performance of Nutritionist\Pediatrician

The diagnosis of the pathology can be made by observing the patient's clinical symptoms in the anamnesis and physical examination, which can present inflammatory processes of atopic dermatitis and eosinophilic esophagitis. Laboratory tests “oral provocation test”, “specific detection test”, “restriction diet” are also required for confirmation (SOLÉ *et al.,* 2012).

After being diagnosed, the child must be accompanied by a nutritionist to carry out the appropriate therapy, avoiding a deficit of calcium, proteins and vitamin D, mitigating clinical symptoms and enabling improvement of the case.

Final considerations

The milk food, whether maternal or of animal origin, is extremely important to reach the recommendations of macro and micronutrients of children, mainly calcium and vitamin D. Pathologies such as lactose intolerance, galactosemia and allergy to cow's milk protein have a therapeutic character of restriction and even the exclusion of this beneficial health food.

Currently, it appears that these dysfunctions have increased sharply. Thus, it is the role of the nutritionist and the pediatrician to be aware of the age ranges that each pathology may affect and to keep up to date with therapies and diagnoses, providing the needs of these infants according to the individual daily recommendations. In addition, they must teach those responsible for their patients to read labels, as erroneous interventions can cause permanent damage.

In general, each patient must be evaluated individually for diagnosis of the pathology and subsequent food prescription, in which a broader and more varied menu in nutrients, minerals and vitamins is provided, one that meets the specific nutritional recommendations of each patient.

Therefore, the multidisciplinary union between nutritionists and pediatricians must be fundamental for an adequate diagnosis and therapy, due to the fact that the pathologies present similar symptoms that make mistakes in the diagnoses and confusion in the interventions.

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