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RISKS OF UNDIAGNOSING FAMILY HYPERCHOLESTEROLEMIA IN CHILDREN: A SYSTEMATIC REVIEW

Júlia Andrade Rodrigues Alves
Institution: Escola Superior de Ciências in Santa Casa de Misericórdia de Vitória (EMESCAM), Vitória-ES
http://lattes.cnpq.br/4389040166457234

Paula Binda Gouvêa
Institution: Escola Superior de Ciências in Santa Casa de Misericórdia de Vitória (EMESCAM), Vitória-ES
http://lattes.cnpq.br/0831969370413709

Victoria Kelbert Lima
Institution: Escola Superior de Ciências in Santa Casa de Misericórdia de Vitória (EMESCAM), Vitória-ES
http://lattes.cnpq.br/5559415448661168

Abstract: Introduction: Familial hypercholesterolemia is an autosomal dominant disease related to lipoprotein metabolism. It is characterized by an increase in cholesterol levels, mainly low-density lipoprotein cholesterol. **Objective:** To identify the main risks that not diagnosing familial hypercholesterolemia in children can pose to their health. **Method:** This is a Systematic Review, carried out from April to June 2019, considering the PubMed/MEDLINE database with MESH (Medical Subject Heading) descriptors: "Hyperlipoproteinemia Type II", "child", "risk groups", "diagnosis". The inclusion criteria in the research were: articles published from 2009 to 2019, in English, French and Portuguese. Exclusion criteria: review articles, case reports, book chapters, articles not available for free and studies carried out with patients over 18 years of age. Given the established parameters, 11 articles were read in full. **Results:** It was analyzed that early diagnosis in children is essential in treatment, helping to prevent cardiovascular diseases. The process of identifying familial hypercholesterolemia can be facilitated through genetic screening techniques among the patient's family members, which evaluates the genetic pattern. Furthermore, some treatment alternatives were established, seeking to discuss the effects of these procedures on pediatric patients. The different types of genetic manifestation and their specific symptoms were other aspects evaluated in the study. **Conclusion:** The importance of early diagnosis in children in the prevention, especially of cardiovascular diseases, was observed. Furthermore, pediatric familial hypercholesterolemia is a subject that requires further studies in order to find new and more effective methods for treatment.

Keywords: Type II hyperlipoproteinemia. Children. Diagnosis. Risk Groups

INTRODUCTION

Familial hypercholesterolemia (FH) is considered an autosomal dominant disease, related to lipoprotein metabolism with a genetic pattern. [1] The disease is characterized by a high increase in cholesterol levels, mainly Low-Density Lipoprotein (LDL), whose manifestations in the body are relevant and require immediate treatment.

[2] Disorders in patients with Heterozygous inheritance (HeFH) reach 1 in every 500 patients worldwide, while disorders in Homozygous patients (HoFH), being much rarer, are presented with a probability of 1/1,000. 000. [1,3] Therefore, Familial Hypercholesterolemia is considered one of the most common genetic diseases in the population. [4] It is also worth highlighting the fact that the disease is primarily asymptomatic, compromising its diagnosis. [1] However, Familial Hypercholesterolemia is capable of progressing to more serious pathologies, mainly cardiovascular diseases, which makes its identification extremely important, especially in childhood cases. Given this scenario, this study aims to investigate, in research, the main risks that not diagnosing hypercholesterolemia in children can pose to their health.

METHODS

This is a systematic review, whose function is to carry out a careful analysis of other literature, in order to gather content from the same area of knowledge in a rigorous way. [5] The study was carried out from April to June 2019, considering the PubMed/MEDLINE database. The descriptors were selected from MESH (Medical Subject Heading), and combined as follows: "Hyperlipoproteinemia Type II" AND child NOT adolescent NOT adult. In the PUBMED database, from the aforementioned combination, 303 articles were found.

The inclusion criteria adopted in the research were: articles published from 2009 to 2019, in English, French and Portuguese. As an exclusion criterion, review articles, case reports, book chapters, articles not available for free in full and studies carried out with patients over 18 years of age were discarded. Given the established parameters, 226 articles were excluded, and 77 were selected for reading the title. After this process, 50 articles were excluded, leaving only 27 for reading the abstracts. After the reading procedure, only 15 articles were filtered to carry out this work. However, 4 of these articles were disregarded due to the fact that they did not provide free access to their full content. In this way, 11 articles were, in fact, read in full.

The selection of articles was made by researchers JA, PG and VL who, together, chose the articles by title and summary, eliminating those that did not fit the objective of the study.

The PRISMA flowchart (Figure 1) shows the stages of the text selection process, according to the inclusion and exclusion criteria adopted, highlighting the number of articles chosen and the reason for the restrictions.

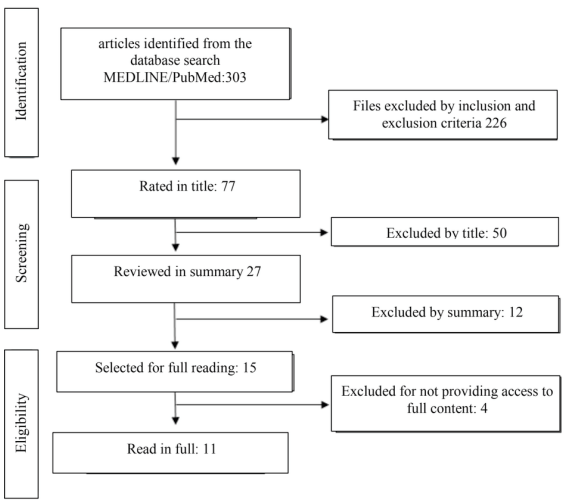

Figure 1. Prism flowchart.

RESULTS AND DISCUSSION

Given the exclusion and inclusion processes, 11 articles were selected to be read in full. From the results obtained, it can be seen that there is a consensus among studies regarding the importance of early diagnosis of familial hypercholesterolemia. Therefore, prior investigation of the disease in pediatric patients significantly reduces the incidence of other illnesses, mainly cardiovascular, increasing the life expectancy of these individuals.[6] One of the studies analyzed in this review concluded that untreated individuals have a 100-fold increased risk of cardiovascular complications compared to those who are unaffected.[7] Among the problems aggravated by familial hypercholesterolemia were atherosclerosis and myocardial infarction, as well as skin and tendon xanthomas. [8]

Despite the difficulty of diagnosis, especially in children, a mechanism that helps the process of identifying the clinical picture is screening for mutations in first-degree relatives who have familial hypercholesterolemia. [7] Using this strategy, cascade genetic screening is carried out, which makes it possible to identify and initiate appropriate treatment, if necessary, according to the genetic history of each patient. This tool is very beneficial for children since, when diagnosed at the right time, they have the possibility of starting treatment before changes in cholesterol levels cause high levels of atherosclerosis. [9]

However, there is controversy among studies on this diagnostic tool. Despite the efficiency of such identification, patients with a negative family history and who had the disease were recognized. [7] Furthermore, it is observed that epidemiological data on familial hypercholesterolemia are predominantly carried out in adults [7], showing the relevance of carrying out studies on this disease in children.

An important symptom that helps in the diagnosis are xanthomas, which are effectively manifested in the homozygous variable of the disease. [10] According to analyzed data, mutations in the LDLR gene are identified in 68% of patients. [4] This clinical manifestation consists of fat deposits in the tendons and skin, formed from the accumulation of cholesterol. Based on studies, it can be seen that Achilles tendon xanthoma is one of the characteristic symptoms of familial hypercholesterolemia, as approximately 30% to 50% of patients with familial hypercholesterolemia present such phenomena. [11] Another relevant point is the fact that individuals diagnosed with familial hypercholesterolemia and who manifest such symptoms have three times the chance of acquiring cardiovascular disease. [8]

Another relevant issue addressed by the articles analyzed is the different treatment alternatives for familial hypercholesterolemia in children. According to the American Academy of Pediatrics (AAP), the use of statins is essential in the treatment of pediatric patients with FH. [4] Guidelines recommend that pharmacological treatment begins at the age of 8 to 10 years.

Furthermore, the importance of carrying out a cautious prescription was highlighted, individually assessing the needs of each individual. [10] In view of a meta-analysis with ten randomized clinical trials, carried out with children and adolescents aged 8 to 18 years, who are undergoing statin therapy, it was possible to observe that these medications significantly reduced LDL-c in these patients. [9] Furthermore, the use of such drugs does not trigger serious side effects, which allows their use from childhood. [10]

In contrast to what was exposed in the aforementioned articles, others consider pharmacological treatment with statins insufficient to reduce LDL-c levels to the required levels, even when combined with other drugs, such as ezetimibe. [12] Thus, the way found to effectively reduce lipid levels consists of the association of statins with lipoprotein apheresis, a procedure that consists of the direct removal of LDL-c from the blood. [13] Through research, it was observed that after the indicated treatment, pediatric patients did not present xanthomas, nor did they manifest any type of cardiovascular disease. Although it has beneficial effects on treatment, LDL-c apheresis has some negative aspects, due to the fact that it is invasive and not widely available. Therefore, in most cases, the frequency of sessions is not sufficient to achieve adequate treatment. [12]

Furthermore, another alternative exposed in the studies was liver transplantation, which should be used in children who have proven cardiovascular diseases and an exacerbated elevation of LDL-c. [12] Although this procedure is a very efficient treatment, it should be used in serious situations, as there are many postoperative risks and it presents certain limitations, mainly related to the lack of donors. [11]

Colesevelam is another pharmacological option, being a synthetic polymer that has the function of sequestering bile salts. This medication forms high-affinity bonds with bile salts in the intestine, which inhibits the reabsorption of this compound. According to the guidelines, colesevelam can be used in the USA in pediatric patients aged between 10 and 17 years with heterozygous familial hypercholesterolemia, and can be administered alone or combined with statins. From studies, the medicine at a dose of 3.75 g/day was well tolerated in pediatric patients with heterozygous familial hypercholesterolemia and showed effective results in reducing LDL-c. [14]

Drug and surgical treatments obtained efficient results in pediatric patients, but when reading the articles, the relationship

between diet, physical exercise and the use of medications were also considered. One of the studies concludes that treatment based on a healthy lifestyle (diet and physical exercise), combined with the use of statins for homozygous children aged 6 to 17 years, is merely insufficient. In children with heterozygous conditions, this type of treatment has proven to be safe and tolerable. [12] Another article, however, evaluated the effectiveness of treating hypercholesterolemia through diet alone. In this context, the consumption of fiber, monounsaturated diets (predominantly vegetable fats) and phytosterols was recommended to consequently reduce LDL and increase HDL. [15] Despite this, all of these articles concluded that physical and eating habits depend on the condition and family history of each pediatric patient, and that they should be controlled for the rest of their lives.

The articles analyzed reflect on the different types of genetic manifestations that this disease can present. The biggest difference noted in the review between patients with heterozygous and homozygous familial hypercholesterolemia was the diagnosis established for each one. Patients who manifest the homozygous character present xanthomas in the skin or tendons [8,11,12], in addition to exhibiting LDL levels approximately double those diagnosed with the heterozygous modality. The prevalence of homozygous familial hypercholesterolemia was for many years considered to be 1:1,000,000, but recently, updated data have recorded it to be around 1:300,000 in northern Europe. [12] Life expectancy, without treatment, of homozygotes does not exceed 20 years of age. Furthermore, as drug treatment is not effective for this condition, liver transplantation is recommended. [11]

CONCLUSION

In view of what has been presented, it is interesting to highlight that early diagnosis of the disease significantly prevents future cardiovascular complications, as it makes it possible to start treatment before lipid levels cause critical implications. Furthermore, it is clear that familial hypercholesterolemia in pediatric patients is an extremely relevant issue, as most existing studies deal with adult patients. Finally, the results indicate that further studies should clarify the most efficient treatments for patients with familial hypercholesterolemia, especially in the long term and assessed individually, seeking not to harm children's lifestyle and ensuring the well-being of this category.

REFERENCES

1. AUSTIN, M. A. Familial Hypercholesterolemia and Coronary Heart Disease: A HuGE Association Review. American Journal of Epidemiology, v. 160, n. 5, p. 421-429, 1 set. 2004. Disponível em: https://doi.org/10.1093/aje/kwh237. Acesso em: 7 fev. 2024.

2. JOURDAN, Claudia *et al.*Normative values for intima–media thickness and distensibility of large arteries in healthy adolescents. **Journal of Hypertension**, v. 23, n. 9, p. 1707-1715, set. 2005. Disponível em: https://doi.org/10.1097/01.hjh.0000178834.26353.d5. Acesso em: 7 fev. 2024.

3. REINER, Z. *et al.*ESC/EAS Guidelines for the management of dyslipidaemias: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). **European Heart Journal**, v. 32, n. 14, p. 1769-1818, 28 jun. 2011. Disponível em: https://doi.org/10.1093/eurheartj/ehr158. Acesso em: 7 fev. 2024.

4. SANTOS, RD *et al.*I Diretriz Brasileira de Hipercolesterolemia Familiar (HF). **Arquivos Brasileiros de Cardiologia**, v. 99, n. 2, p. 1-28, 2012. Disponível em: https://doi.org/10.5935/abc.20120202. Acesso em: 7 fev. 2024.

5. JULIAN, Higgins; PROF, Green Sally; COLLABORATION, Cochrane (ed.). Cochrane handbook for systematic reviews of interventions. Chichester, West Sussex: John Wiley & Sons, 2008. ISBN 9780470699515.

6. HARADA-SHIBA, Mariko *et al.*Guidance for Pediatric Familial Hypercholesterolemia 2017. Journal of Atherosclerosis and Thrombosis, v. 25, n. 6, p. 539-553, 1 jun. 2018. Disponível em: https://doi.org/10.5551/jat.cr002. Acesso em: 7 fev. 2024.

7. KLANČAR, Gašper *et al.*Universal Screening for Familial Hypercholesterolemia in Children. **Journal of the American College of Cardiology**, v. 66, n. 11, p. 1250-1257, set. 2015. Disponível em: https://doi.org/10.1016/j.jacc.2015.07.017. Acesso em: 7 fev. 2024.

8. REICHWALDT, Ilona *et al.*Differential diagnosis of tendon tumors: xanthomas caused by hyperlipidemia in children. **Journal of Pediatric Surgery**, v. 45, n. 10, p. e9-e12, out. 2010. Disponível em: https://doi.org/10.1016/j.jpedsurg.2010.06.030. Acesso em: 7 fev. 2024.

9. ANTONIAZZI, Luiza. Can Non-Pharmacological Treatment Promote Additional Benefit for Children with Familial Hypercholesterolemia Treated with Statins? **Arquivos Brasileiros de Cardiologia**, 2018. Disponível em: https://doi.org/10.5935/abc.20180235. Acesso em: 7 fev. 2024.

10. MIYAGI, Yoshitsune; HARADA-SHIBA, Mariko; OHTA, Takao. Effect of Statin Therapy in 4-Year-Old Dichorionic Diamniotic Twins with Familial Hypercholesterolemia Showing Multiple Xanthomas. **Journal of Atherosclerosis and Thrombosis**, v. 23, n. 1, p. 112-117, 2016. Disponível em: https://doi.org/10.5551/jat.31666. Acesso em: 7 fev. 2024.

11. SANNA, Claudia *et al.*Homozygous familial hypercholesterolemia in childhood: Genotype-phenotype description, established therapies and perspectives. **Atherosclerosis**, v. 247, p. 97-104, abr. 2016. Disponível em: https://doi.org/10.1016/j.atherosclerosis.2016.02.009. Acesso em: 7 fev. 2024.

12. REINER, Željko. Treatment of children with homozygous familial hypercholesterolaemia. European Journal of Preventive Cardiology, v. 25, n. 10, p. 1095-1097, 6 jun. 2018. Disponível em: https://doi.org/10.1177/2047487318781360. Acesso em: 7 fev. 2024.

13. PALMA, Isabel *et al.*LDL-aférese no tratamento de hipercolesterolemia familiar: experiência do Hospital Santo António. **Revista Portuguesa de Cardiologia**, v. 34, n. 3, p. 163-172, mar. 2015. Disponível em: https://doi.org/10.1016/j.repc.2014.07.007. Acesso em: 7 fev. 2024.

14. MISIR, Sam *et al.*Efficacy and Safety of Colesevelam HCl in Pediatric Patients with Heterozygous Familial Hypercholesterolemia. **Journal of Clinical Lipidology**, v. 3, n. 3, p. 220, maio 2009. Disponível em: https://doi.org/10.1016/j.jacl.2009.04.021. Acesso em: 7 fev. 2024.

15. TERSHAKOVEC, Andrew M. *et al.*Dietary recommendations for children. **The American Journal of Clinical Nutrition**, v. 62, n. 2, p. 443-445, 1 ago. 1995. Disponível em: https://doi.org/10.1093/ajcn/62.2.443a. Acesso em: 7 fev. 2024.