INTEGRATIVE REVIEW OF THE LITERATURE

Treatment of child with phenylketonuria: a literature review

Triagem neonatal e tratamento de criança com fenilcetonúria: uma revisão integrativa da literatura

Tratamento do niño con fenilcetonuria: una revisión de la literatura

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ABSTRACT

Objective: To analyze the importance of Neonatal Screening for the treatment of children with phenylketonuria. Method: This is an integrative review. To select the studies we looked at the electronic databases Scientific Electronic Library Online - SciELO journal portal and CAPES in September 2013, using the keywords: Phenylketonuria, Triage, Child health. Results: The analysis of the articles indicated that in the period 2008-2013, the year 2010 had the highest number of publications. Most studies paused to examine the importance of neonatal screening program to evaluate the tracking phenylketonuria, as well to characterize the performance of children diagnosed and treated early with phenylketonuria. Conclusion: Studies have shown that treatment is significantly more effective when deployed in pre-clinical stage of the disease and there is a screening test, the screening test, which is simple, efficient, applicable on a large scale and low cost. Descriptors: Phenylketonuria, Triage, Child health.

RESUMO


RESUMEN

Objetivo: Analizar la importancia de la Triagem Neonatal para el tratamiento de los niños con fenilcetonuria. Método: Se trata de una revisión integradora. Para seleccionar los estudios que analizamos las bases de datos electrónicas Scientific Electronic Library Online - Portal de la revista SciELO y CAPES en septiembre de 2013, utilizando las palabras clave: Fenilcetonuria, Triaje, Salud del Niño. Resultados: El análisis de los artículos se indica que en el periodo 2008-2013, el año 2010 tuvo el mayor número de publicaciones. La mayoría de los estudios se detuvieron para examinar la importancia del programa de cribado neonatal para evaluar los fenilcetonuria seguimiento, así como para caracterizar el rendimiento de los niños son diagnosticados a tiempo con fenilcetonuria. Conclusión: Los estudios han demostrado que el tratamiento es significativamente más eficaz cuando se despliega en la etapa de pre-clínica de la enfermedad y hay una prueba de detección, la prueba de detección, que es simple, eficaz, aplicable a gran escala y bajo costo. Descriptores: Fenilcetonuria, Triaje, Salud del niño.
Phenylketonuria (PKU) is the most common of the inborn errors of amino acid metabolism. Due to a deficiency of phenylalanine hydroxylase, the enzyme that catalyzes the conversion of phenylalanine to tyrosine. The introduction of a diet low in phenylalanine should begin in the first months of life, preferably in the first month, to prevent mental retardation and more severe manifestation of the disease.¹

The hyperphenylalaninemia (HPA), the generic name given to high levels of phenylalanine (Phe) in blood, is a primary disorder of the hepatic enzyme phenylalanine hydroxylase (PAH) or enzymes that synthesize or reduce the tetrahydrobiopterin coenzyme.²

Phenylalanine is an essential aromatic amino acid, mainly metabolised in the liver. Phenylalanine which is not required for protein anabolism, tyrosine is hydroxylated by phenylalanine hydroxylase. This has a quaternary structure having four polypeptide chains, each connected to an iron atom, that binds oxygen, to form tyrosine.³

Different types of hyperphenylalaninemia can be found, according to the metabolic error involved, forming a heterogeneous group of diseases, including phenylketonuria (PKU) and classical variations of hyperphenylalaninemia (PAHs), as persistent HPA, the mild HPA and atypical PKU.⁴

Currently in the healthcare scenario phenylketonuria has been diagnosed through neonatal screening tests, popularly known as the Guthrie Test, which is mandatory throughout the country since the 80s, after the implementation of the National Neonatal Screening Program (NNSP). Thus, all newborns should undergo this test for screening of some metabolic abnormalities, including phenylketonuria, targeting the immediate initiation of treatment.⁵,⁶

The phenylketonuric subjects are clinically normal at birth, beginning to manifest developmental delays around 6 months of age, with spasms, hypotonia, and rash. Display reduced pigmentation, microcephaly and epilepsy. The excretion of phenylketones provides the urine the characteristic odor.⁷

However, it is known that Brazil is ethnically, socially and economically marked by numerous inequalities, making difficult the establishment and development of health programs, as an example of Neonatal Screening for the treatment of phenylketonuria. Thus, the success and effectiveness of neonatal screening programs depend mainly on the involvement of health authorities, educational campaigns including healthcare professionals and the population and investments.

Given this issue the study aims to analyze the importance of Neonatal Screening for the treatment of children with phenylketonuria.

This study is an integrative review. For its construction the following steps were covered: establishment of hypothesis and objectives of the integrative review, establishment of criteria for inclusion and exclusion of articles (sample selection); definition of information to be extracted from the selected articles, analysis of results, discussion and presentation the results and the last stage consisted of submitting the review.⁸
Moura GCB, Carvalho JO, Carvalho FG et al. The guiding question for the construction of this integrative review was “What is the importance of Neonatal Screening for the treatment of phenylketonuria?”. To select the references we looked at the electronic databases Scientific Electronic Library Online - SciELO and Periodical Portal CAPES in September 2013.

In search for articles by standardized Descriptors in Health Sciences Headings (DECs) were to be used descriptors, which were: Child and neonatal phenylketonuria.

After application of the descriptors the following results were found: in the database SCIELO sixty-six (26) Articles and Portal CAPES center and eighty (180) articles. The articles were subjected to cuts, which may be below Viewed in figure 1.

![Figure 1: search the banks of SCIELO and CAPES Portal Data Strategy. Teresina, 2013](image)

Following the electronic search, in order to identify items considered relevant and exclude those who did not meet the inclusion criteria, were selected survey regarding guiding question, full text, with humans (children), with reference to treatment of children with phenylketonuria and published since 2008.

After identifying the related study material sorting the items, by reading the titles and abstracts was performed. Being excluded from jobs as editorials, thesis, dissertations, book reviews and interviews. After this step remained for the final sample of this review 14 articles. Studies that met the inclusion criteria were obtained in full.

For the final analysis of the study an instrument that includes the following items was prepared: identifying the original article, methodological characteristics of the study, assessment of the methodological rigor of interventions measured and the results. In the next step, the data were subjected to critical analysis and further discussion and description of the results.

RESULTS AND DISCUSSION

Frame 1 presents data on the articles analyzed for year, database, the publication title and magazines. The results indicated that 14 articles were published in the period 2008-2013, with the year 2010 a large number of publications with four, followed by 2009 and 2012 with three two respectively. Have 2011 and 2013 had two publications each year. In reference to thematic of 2008 showed up with smaller publication, highlighting just one article.

Regarding indexing of publications related to the theme was highlight the database SCIELO with nine published articles, followed by CAPES Portal with five. The more related to disclosures of research journal was the Brazilian Metabolic Endocrinology file with three articles and the rest were distributed in different journals that are synoptically highlighted in the table below.
Frame 2 is envisioned that the studies stopped to check the importance of screening of children diagnosed with PKU, the clinical and epidemiological characteristics, treatment, causes, demographic characteristics and clinical findings. Thus, the main objectives were related to: verify the importance of newborn screening for metabolic disorders and to evaluate the preventive and health promotion of children with phenylketonuria actions, analyze the causes, symptoms and dietary treatment of PKU infants; assess the national and international prevalence of phenylketonuria; characterize the performance, clinical and demographic characteristics of children with phenylketonuria.

J. res.: fundam. care. online 2013.dec. 5(6): 363-371

In reference to the results of the studies can be inferred that the same reported various aspects of the importance of newborn screening, referring to the main consequences brought about by the condition and the effectiveness of the screening program to treat the disease, among other relations presented in frame 3.
After analysis it was realized that Brazil has a Newborn Screening Program that follows international guidelines, which appears to be irreversible, since it represents a considerable technical advance, being known worldwide as the largest public health program linked to genetics. But its consolidation is subject to certain medical and ethical issues that need to be discussed, because the progress of the program are new challenges as new issues and diseases are introduced into the diseases screened panel.¹³

But to the Newborn Screening Program can fully achieve its objectives, it is essential that some goals are met, as: collection of the blood sample obtained properly and in adequate time; fast referral of sample to the reference laboratory, conduct of examinations by laboratory obeying strict quality control, quick communication of test results; reference center endowed with doctor(s) trained(s) to establish (in) accurate diagnosis and structure for clinical follow-up of affected children; periodic evaluations of the quality program, reporting their results to the authorities, so that any improvements can be implemented.¹⁰

Thus, is emphatic to highlight that the process of newborn screening is not limited to collecting material for analysis, but is secondary to this, because without the dialogue with the other aforementioned steps, the program is limited and its proposal for early screening for the actual outcome / treatment and prevention of sequelae for child development become ineffective.¹¹

Furthermore, within your functioning healthcare team involved has a role of great value, especially pediatricians and speech therapists occupy an important position in the treatment, the possible changes in referrals and improving the quality of life of these children, however data show that scientific knowledge pediatrician about the diseases screened, treatment and prognosis is still not concrete hampering the progress and establishment of some program issues, as well as effective treatment of children with phenylketonuria through diagnostic screening.⁹,¹²

Nationwide access to newborn screening is very heterogeneous, for example, in 2007 in the state of Rio de Janeiro coverage reached 80.7%, unlike other cities.¹³,¹⁴ Therefore, the involvement of health, government and local authorities and professional societies are critical milestones, not

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Nationwide access to newborn screening is very heterogeneous, for example, in 2007 in the state of Rio de Janeiro coverage reached 80.7%, unlike other cities.¹³,¹⁴

Thus, states with less government involvement have a lower coverage, and those who have a position where the respective administrative bodies are more active, have greater coverage. Therefore, the involvement of health, government and local authorities and professional societies are critical milestones, not
Moura GCB, Carvalho JO, Carvalho FG et al. only for the scope of coverage, but also with respect to the degree of opportunity of the collections.¹¹

In this perspective it is important to emphasize that the Newborn Screening Program continually goes through reviews should meet the minimum requirements recommended by the Ministry of Health in the state of Tocantins, for example, the data indicate a significant evolution of the coverage rate, showing that the prevalence of diseases such as phenylketonuria and congenital hypothyroidism possessed lower rate than the national average, in turn, in Santa Catarina phenylketonuria was lower than the national prevalence, while the second condition was similar to global and national values.¹⁵,¹⁶

Also according to program evaluations collection of the first blood sample and initiation of treatment in many cases still occurs at a higher time than recommended by the Ministry of Health and delays that accumulate in various stages of the screening process can nullify the benefits of early detection, precept of a neonatal screening program.¹⁴ Despite this evidence in literature suggests a positive perception of parents about the deployment, quality and evolution of the Newborn Screening Program, but there is controversy about the need for greater government support for such a program is optimized and can advance to the next stages.¹⁶

In this regard it is worth noting that the Newborn Screening Program is critical both for early screening of diseases that previously were not known, especially PKU, but mainly for the improvement and reduction in infant mortality from other diseases of genetic imprint.

But the early screening of diseases such as phenylketonuria achieved by the program does not guarantee a cure, as an example, it is important to highlight that individuals with phenylketonuria, even with early treatment, may show changes in cognitive functions, language, motor and social-behavioral. Thus scientific findings justify the referral of new proposals to the Ministry of Health with a view to hiring Speech Therapists in Newborn Screening Programs credentialed for full monitoring of individuals with this condition, ensuring less commitment and more effective treatment.¹⁷

Moreover, even with treatment and appropriate follow-up is still physiological changes caused primarily by dietary treatment, resulting from the disability and severe restriction on the consumption of foods containing the amino acid phenylalanine and secondary to this, other nutrients. This results in low intake of several nutrients, including selenium and calcium. Even with supplementation with formulas that seek to meet the needs of vitamins, minerals and essential amino acids, nutritional deficiencies are not discarded.¹⁸,¹⁹

However, scientific evidence showed that dietary treatment did not influence physiological changes in children with phenylketonuria, with an emphasis on auditory changes. Thus more studies showing the relationship of certain mixtures to recover possible deficiencies found and to ensure treatment and quality of life more suited to patients with phenylketonuria is needed.¹²

It is unquestionable that the Newborn Screening Program is extremely relevant for screening and early treatment of children diagnosed with PKU, however is noticeable through the scientific literature that changes accompanying the life cycle of these individuals, especially in the personal-social interaction, language and fine motor adaptive. In this sense, its long development is marked by changes that continually undermine your communication, social integration and learning.²⁰

Thus the strengthening of the management of current health care to the
Moura GCB, Carvalho JO, Carvalho FG et al. minimum requirements of the program in order to mimic the delay in diagnosis and increase the initiation of treatment for confirmed cases of diseases for diagnostic screening with special look is needed in this research for phenylketonuria, seeking to develop strategies to improve the operation, promoting a greater agility in the whole process and the start of treatment occurs in adequate time.\textsuperscript{21,22}

**CONCLUSION**

Studies have shown that treatment is significantly more effective when deployed in the preclinical phase of the disease, because of their minimum requirements and maintaining its efficiency applicable on a large scale and low cost.

It is inferred after analysis that the Newborn Screening Program is extremely relevant for screening and early treatment of children diagnosed with PKU, but this does not guarantee a cure, since genetic diseases deserve further studies and even with proper treatment still there is the presence of many losses in lives of children with phenylketonuria, especially in personal-social, language and adaptive fine motor areas. Thus, it is hoped through this study a contribution to scientific production and fostering new research related to this theme.

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J. res.: fundam. care. online 2013.dec. 5(6): 363-371


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Received on: 10/07/2013
Required for review: no
Approved on: 25/10/2013
Published on: 27/12/2013

J. res.: fundam. care. online 2013.dec. 5(6): 363-371