THE IMPORTANCE OF NEWBORN SCREENING FOR THE DIAGNOSIS OF CONGENITAL ADRENAL HYPERPLASIA: LITERATURE REVIEW

A IMPORTÂNCIA DA TRIAGEM NEONATAL PARA DIAGNÓSTICO DA HIPERPLASIA ADRENAL CONGÊNITA: REVISÃO DE LITERATURA

LA IMPORTANCIA DEL TAMIZAJE NEONATAL PARA EL DIAGNÓSTICO DE LA HIPERPLASIA SUPRARRENAL CONGÉNITA: REVISIÓN DE LA LITERATURA

Paula Ho Parreira¹
Emma Patrice Ruppert²
Maria Fernanda Amaral Carvalho³
Mariana Costa Ferreira Righi Rodrigues⁴
Pedro Rabelo Dutra⁵

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ABSTRACT
Introduction: Congenital adrenal hyperplasia (CAH) is a metabolic condition that involves many different clinical manifestations and specificities, caused by genetic abnormalities that are associated with phenotypic enzyme deficiencies. It is one of the many pathologies included in the Brazilian newborn screening, demonstrating its importance.

Objectives: Present a bibliographic review about the importance of newborn screening in diagnosing CAH, emphasizing the physiopathology of the disease and its epidemiologic and social relevance. Method: A literature review was done using the following databases: Biblioteca Virtual em Saúde (BVS), Scielo, PubMed and Lilacs.

Results: The early diagnosis of CAH is crucial to the reduction of complications from this pathology, being that the neonatal screening is mainly aimed at detecting the classic salt-wasting form that is the most serious and potentially life-threatening form for the child.

¹ Graduated in Medicine from Faculdade Ciências Médicas de Minas Gerais. Alameda Ezequiel Dias, 275, Centro, Belo Horizonte - MG, CEP: 30130-110. E-mail: phoparreira@gmail.com
² Graduated in Medicine from Faculdade Ciências Médicas de Minas Gerais. Alameda Ezequiel Dias, 275, Centro, Belo Horizonte - MG, CEP: 30130-110. E-mail: ruppertemmap@gmail.com
³ Graduated in Medicine from Faculdade Ciências Médicas de Minas Gerais. Alameda Ezequiel Dias, 275, Centro, Belo Horizonte - MG, CEP: 30130-110. E-mail: nandaamaral31@gmail.com
⁴ Graduated in Medicine from Faculdade Ciências Médicas de Minas Gerais. Alameda Ezequiel Dias, 275, Centro, Belo Horizonte - MG, CEP: 30130-110. E-mail: mari.righi@gmail.com
⁵ Graduated in Medicine from Faculdade Ciências Médicas de Minas Gerais. Alameda Ezequiel Dias, 275, Centro, Belo Horizonte - MG, CEP: 30130-110. E-mail: pedrorabelod@gmail.com
Conclusion: Expanding the screening tests and making them more widely available to the population is essential to minimize the risks.

Keywords: Congenital Adrenal Hyperplasia; newborn screening; early diagnosis.

RESUMO
Introdução: A hiperplasia adrenal congênita (HAC) é uma condição metabólica que abrange diversas manifestações clínicas e especificidades, sendo decorrente de anormalidades genéticas que se associam a deficiências fenotípicas enzimáticas. É uma das diversas patologias incluídas nos testes de triagem neonatal no Brasil, mostrando sua significância. Objetivos: Apresentar uma revisão bibliográfica sobre a importância da triagem neonatal no diagnóstico da hiperplasia adrenal congênita (HAC), enfatizando a fisiopatologia da doença e sua relevância epidemiológica e social. Métodos: Realizada revisão da literatura, com as seguintes bases de dados: biblioteca virtual em saúde (BVS), Scielo, PubMed e Lilacs. Resultados: O diagnóstico precoce da HAC é crucial para a redução das complicações derivadas dessa patologia, sendo que a triagem neonatal visa principalmente a detecção da forma clássica perdedora de sal que é a forma mais grave e com potencial risco de vida para a criança. Conclusão: Ampliar os testes de triagem e disponibilizá-los com maior abrangência para a população é essencial para minimizar os riscos.

Palavras-chave: Hiperplasia Suprarrenal Congênita; triagem neonatal; diagnóstico precoce.

RESUMEN
Introducción: La hiperplasia adrenal congénita (HAC) es una condición metabólica que abarca diversas manifestaciones clínicas y especificidades y se deriva de las anomalías genéticas asociadas a las deficiencias fenotípicas enzimáticas. Es una de las diversas patologías incluidas en las pruebas de detección neonatal en Brasil, lo que demuestra su importancia. Objetivos: Presentar una revisión bibliográfica sobre la importancia del triaje neonatal en el diagnóstico de hiperplasia adrenal congénita (HAC), enfatizando la fisiopatología de la enfermedad y su relevancia epidemiológica y social. Métodos: Se revisó la literatura con las siguientes bases de datos: Biblioteca virtual sobre salud (BVS), Scielo, PubMed y Lilacs. Resultados: El diagnóstico precoz de HAC es crucial para la reducción de complicaciones derivadas de esta patología, con el control neonatal principalmente dirigido a detectar la forma clásica de perdedor de sal, que es la forma más grave y potencialmente amenazante para la vida del niño. Conclusión: La extensión de las pruebas de detección y su mayor difusión entre la población es esencial para reducir al mínimo el riesgo.

Palabras clave: Hiperplasia Suprarrenal Congénita; triage neonatal; diagnóstico temprano.

1. Introduction

Newborn screening tests consist of laboratory exams done from blood samples in a population aged between 0 and 30 days of life. The purpose of this screening is not to diagnose a disease, but to separate neonates into two groups: those with high probability of having a certain pathology and those with lower
probability. To do this, it is important that these tests have a high sensitivity to avoid false-negatives and at least a reasonable specificity to minimize false-positives. \(^1\)\(^2\)

In the early 1960s, the North American physician and microbiologist Robert Guthrie (1916-1995) proposed the method of newborn screening using a bacterial inhibition assay performed with blood samples collected on high absorption paper, in order to detect concentrations of the amino acid phenylalanine. Guthrie was aiming to identify phenylketonuric individuals before symptomatology occurred, since the neurological damage caused by the ingestion of this amino acid by sick people was irreversible. Considering the american physician's goal, newborn screening was steadily improved and later adapted for several other metabolic diseases, including congenital adrenal hyperplasia (CAH). \(^2\)\(^3\)

Congenital adrenal hyperplasia is a group of syndromes with an autosomal recessive genetic inheritance characterized by enzyme deficiencies that are vital in the production of adrenal steroid hormones. About 95\% of the occurrences of these diseases are due to a deficiency of 21-hydroxylase, and approximately 5\% of the cases are due to a lack of 11-beta-hydroxylase. This is important because the clinical manifestations of this disease depend on which enzyme is involved and the degree of its deficiency. From this premise, the patient can develop insufficiencies or excesses of glucocorticoid (mainly cortisol), mineralocorticoid (mainly aldosterone) and/or androgen hormones. \(^4\)

The incidence of CAH worldwide is 1:15.000 live births, and in Brazil it ranges from 1:7.500 to 1:10.000. The most frequent syndromes of CAH are: the classic salt-wasting type, the classic non-salt-wasting type, and the non-classic type. Since approximately 65-75\% of children have the classic salt-wasting type, this is the main target of newborn screening, performed by detecting high levels of 17-hydroxyprogesterone (17OHP), 21-hydroxylase's normal substrate, on filter paper. Moreover, if not treated early, this syndrome presents high morbidity and mortality rates, and female individuals may also present ambiguous genitalia at birth, which can lead to incorrect civil registries. Thus, the importance of the methodology and the development of newborn screening for Congenital Adrenal
Hyperplasia is evidenced, and early diagnosis can contribute to the reduction of complications.4,5

2. Methods

The present study is a literature review, using the databases Virtual Health Library (VHL), Scielo, PubMed and Lilacs. For this search the following descriptors were used: "Congenital adrenal hyperplasia", "Newborn screening" and "Early diagnosis", covering research published in Portuguese and English. Articles published from the year 2005 to 2021 were included in this study.

3. Results

Table 1 – 17OH progesterone in CAH screening.

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Title</th>
<th>Type of study</th>
<th>Objectives</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alves, Júnior e Toralles (2006)</td>
<td>Neonatal screening for congenital adrenal hyperplasia: considerations regarding the transient rise of the 17-hydroxyprogesterone</td>
<td>Retrospective experimental study n=10.</td>
<td>To investigate the transient rise in 17-OHP diagnosed by newborn screening test that, in some cases, may lead to the incorrect diagnosis of congenital adrenal hyperplasia.</td>
<td>It was concluded that NST using only two reference values for 17-OHP (full-term newborns and pre-term) may yield false-positives results.</td>
</tr>
<tr>
<td>Barra et al. (2012)</td>
<td>Neonatal screening for congenital adrenal hyperplasia</td>
<td>Analytical observational study.</td>
<td>Contribute to the advances in newborn screening for CAH by analyzing the cutoff point of 17OHP measures with adequate cost-effectiveness.</td>
<td>The use of 17OHP cutoff values, considering birth weight, proved to be a cost-effective measure to reduce false positives results for 17OHP, which benefits children.</td>
</tr>
<tr>
<td>Cardoso et al. (2005)</td>
<td>Congenital adrenal hyperplasia newborn screening: Rio de Janeiro experience</td>
<td>Descriptive observational study</td>
<td>To determine 17OH progesterone (17OHP) levels in the newborn screening for Congenital Adrenal Hyperplasia due to 21 hydroxylase deficiency (CAH-21OHD).</td>
<td>Confirms that 17OHP analysis was a reliable test to CAH-21OHD new-born screening and was able to differen-tiate between healthy infants and those with the classical form of CAH-21OHD.</td>
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* Results found in the review of articles from 2005 to 2021. 17ohpuse of 17OH progesterone in CAH screening. Source: self-authored
### Table 2 – Treatment and molecular testing for CAH.

<table>
<thead>
<tr>
<th>Author/Year</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Leite et al. (2008)</td>
<td>Comparative study of prednisolone versus hydrocortisone acetate for treatment of patients with the classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency</td>
<td>Experimental study n=15.</td>
<td>To compare the efficacy of oral prednisolone and oral hydrocortisone in the treatment of CAH due to 21-hydroxylase deficiency</td>
<td>It was concluded that prednisolone administered once a day orally has similar efficacy to that obtained with hydrocortisone used three times a day, and may be considered a therapeutic option in patients with CAH due to 21-hydroxylase deficiency.</td>
</tr>
<tr>
<td>Merke (2008)</td>
<td>Approach to the Adult with Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency.</td>
<td>Descriptive observational case report study.</td>
<td>To analyze the existing procedures for the treatment of CAH, especially in the classical form in order to treat an 18-year-old patient.</td>
<td>After analyzing all the data it is believed that the best option would be the administration of glucocorticoids without harming their reproductive, sexual or bone health.</td>
</tr>
<tr>
<td>Prado (2016)</td>
<td>Detection of CYP21A2 gene mutations in children with suspected Congenital Adrenal Hyperplasia in the State of Rio Grande do Sul.</td>
<td>Analytical observational study.</td>
<td>To apply molecular methodologies for the analysis of children with suspected CAH in the state of Rio Grande do Sul.</td>
<td>Identification of 84 pathogenic alleles in 48 patients, and the most frequent mutations found were p.Val281Leu (27.1%) and IVS2-13A/C&gt;G (20.8%), in order to show the efficiency of the methodologies used in the work for the detection of the most frequent mutations in Brazil.</td>
</tr>
</tbody>
</table>

*Therapeutic alternatives and use of molecular tests for diagnosis of CAH.

Source: self-authored

### Table 3 – Experiences of neonatal screening for CAH.

<table>
<thead>
<tr>
<th>Author/Year</th>
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<th>Type of study</th>
<th>Objectives</th>
<th>Results</th>
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<tbody>
<tr>
<td>Kopacek et</td>
<td>Development and</td>
<td>Descriptive</td>
<td>To describe the</td>
<td>It was observed that</td>
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</table>

*Therapeutic alternatives and use of molecular tests for diagnosis of CAH.*

Source: self-authored
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<table>
<thead>
<tr>
<th>Authors</th>
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<th>Type of Study</th>
<th>Objectives</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td>al. (2015)</td>
<td>functioning of the National Neonatal Screening Program in the state of Rio Grande do Sul from 2001 to 2015.</td>
<td>observational study</td>
<td>experience of the Newborn Screening Reference Service in Rio Grande do Sul (SRTN-RS) since its implementation in 2001 at Hospital Materno-Infantil Presidente Vargas (HMIPV) until the first quarter of 2015.</td>
<td>from 2007 to 2014, there was an increase from 36% to 83% in the number of babies who underwent neonatal screening in the first week of life.</td>
</tr>
<tr>
<td>Kopacek et al. (2019)</td>
<td>Clinical and molecular profile of newborns with confirmed or suspicious congenital adrenal hyperplasia detected after a public screening program implementation.</td>
<td>Cross-sectional study.</td>
<td>To describe the results obtained in a newborn screening program after its implementation and evaluate the clinical and molecular profiles of confirmed and suspected cases of congenital adrenal hyperplasia.</td>
<td>15 classic cases of CAH were diagnosed in a total of 217,965 newborns. Of 132 patients, 7 non-classical and 14 heterozygous patients were screened for CYP21A2 mutations, and 96 patients had false positives with wild-type CYP21A2. In the new tests, increased levels of 17-hydroxyprogesterone were found in patients with classic CAH and showed significant correlation with genotype-related classic CAH. The most frequent mutations were IVS2-13A&gt;C&gt;G, deletion or gene rearrangement events in the classical form. In the non-classical and the heterozygous disease, p.Val282Leu was the most common mutation.</td>
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</tbody>
</table>

*Description of experiences and results obtained from neonatal screening for CAH.
Source: self-authored

Table 4 – Psychosocial aspects involved in CAH and its screening.

<table>
<thead>
<tr>
<th>Author/Year</th>
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<th>Type of study</th>
<th>Objectives</th>
<th>Results</th>
</tr>
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<tbody>
<tr>
<td>Mallmann, Tomasi and Boing (2020)</td>
<td>Neonatal screening tests in Brazil: prevalence rates and</td>
<td>Cross-sectional study.</td>
<td>Identify the prevalence and associated factors with the performance of the heel prick test in Brazil at any time of life was 96.5%. The performance of the test was significantly higher among</td>
<td></td>
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<tr>
<td>Source</td>
<td>Study Title</td>
<td>Methodological Approach</td>
<td>Findings</td>
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<tr>
<td>Spencer et al. (2021)</td>
<td>Prenatal androgen exposure and children’s gender-typed behavior and toy and playmate preferences</td>
<td>Analytical observational study.</td>
<td>Children whose mothers or guardians reported higher per capita household income and who had private health insurance (p &lt; 0.001). There was no statistically significant difference regarding the performance of the tests according to skin color/ethnicity (p &gt; 0.05).</td>
<td></td>
</tr>
<tr>
<td>Telles-silveira et al. (2009)</td>
<td>Congenital adrenal hyperplasia: a qualitative study on disease and treatment, doubts, anguishes and relationships</td>
<td>Experimental study n=21.</td>
<td>Girls with CAH scored in a more male-typical direction compared to unaffected girls. They also show a greater interest in having boys as playmates. Finally, the study found no significant within-sex correlations between amniotic fluid testosterone and any of the study measures, suggesting that amniotic fluid testosterone may be a relatively insensitive measure of prenatal androgen exposure.</td>
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</tbody>
</table>

*Analysis of the psychosocial aspects involved in the illness and screening for CAH from different points of view.

Source: self-authored

**4. Discussion**

**4.1 Pathophysiology of Congenital Adrenal Hyperplasia**

CAH is an autosomal recessive disease and in 90-95% of the cases it is caused by a deficiency in the enzyme 21-hydroxylase which impairs the production of cortisol and aldosterone. Secondarily, the production of corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH)
by the hypothalamus and pituitary gland, respectively, is impaired due to negative feedback. Consequently, the adrenal gland suffers hyperplasia and, considering that the production of sex steroids does not require the 21-hydroxylase enzyme for their production, these hormones end up being produced in excessive amounts.  

Sex steroids are precursors of the androgen’s testosterone and dihydrotestosterone, and also help in the formation of estrogens. For this reason, this disease is also the most common cause of ambiguous genitalia. In addition, about 75% of patients cannot synthesize enough aldosterone to maintain sodium levels in the body, leading to bouts of salt loss that can lead to life-threatening hyponatremic dehydration.  

A large portion of cases occur due to mutations in the CYP21A2, the gene encoding 21-hydroxylase, and clinical manifestations may be different due to variable enzyme activity. More than one hundred mutations in this gene have been found to account for deficiency of this enzyme. Some of these mutations result from a genetic material exchange between the CYP21A2 gene and a similar DNA fragment called a pseudogene, which differs by approximately 65 nucleotides but is not functional. This pseudogene is located very close to the CYP21A2 gene on chromosome 6. The type of DNA exchange that takes place is called gene conversion. The genetic material in the pseudogene contains errors that, when introduced into the CYP21A2 gene, disrupt the way in which the gene’s instructions are used to produce a protein. Other mutations that cause 21-hydroxylase deficiency act by altering the structural components of a single protein in the enzyme, or by deleting or inserting pieces of DNA into the CYP21A2 gene. 

CAH can be divided into classical type, subdivided into salt-losing and simple virilizing, and non-classical type, depending on the type and intensity of the enzymatic alteration.

The classic form is characterized by extremely low enzyme activity, ranging from 0 to 1%, and the clinical aspects already begin in the prenatal period, and can be identified soon after birth. Female patients have variable degrees of virilization at birth, and male patients have normal or enlarged
genitalia. Among the subdivisions of classic CAH, the salt-losing type is the most common and the most severe, with the enzyme completely non-functional. In this most severe presentation, aldosterone deficiency causes dehydration, with hyponatremia and hyperkalemia from the second week of life, and is called a salt wasting crisis. Cortisol deficiency decreases carbohydrate metabolism and the pressure effect of catecholamines, which causes the exacerbation of shock. There is an excess of androgens due to the accumulation of adrenal precursors, mainly 17 OH-progesterone, which will undergo the action of other adrenal enzymes. It is observed that this excess already occurs intrauterine, being able to lead to the virilization of the external female genitalia. Thus, 46XX newborns will present with ambiguous genitalia, while 46XY newborns may present with hyperpigmentation of the genital region and enlargement of the penis that are generally not noticed at birth, which is why this latter group presents the highest risk of not being diagnosed. In the case of the classic simple virilizing form, patients have prenatal virilization with elevated levels of androgens and steroid precursors, and preserved aldosterone production.7,9,10

In the non-classical form, however, carriers of the disease may remain asymptomatic or develop mild signs of androgen excess at any stage of life.9

4.2 Treatment of CAH

The treatment of classic CAH in children include glucocorticoids (GC), with the aim of correcting the cortisol deficiency, as well as improving the quality of life and reducing morbidity and mortality rates associated with this disease. However, if the GC are administered in physiological levels, they are unable to suppress the production of corticotropin and androgens, for this reason they are given in excessive amounts which may cause hypercortisolism and/or an excess of androgens. Typically, the recommended dose of hydrocortisone is 10-15 mg/m^2 two to three times a day. There is also a tendency to avoid long-acting GC in children, given their potential to suppress the child's growth, evidenced by a long-term study following patients with CAH that did not achieve their target height. In adults, the use of long-acting GC is preferred, because they are highly effective and can be used once or twice a day. There is a greater variety of drugs to
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choose from in adults, such as: hydrocortisone, prednisone, prednisolone, dexamethasone or even a combination of these. This increased variety of medications allow the patient to have a greater influence on the choice of treatment. 11,12

Currently, no medication is able to simulate the circadian rhythm of cortisol production. This cycle consists of a peak of production during the morning and a subsequent decline. Therefore, it is still unsure which is the best time of day to administer the drug and at which period it should be given in larger amounts. 12

To treat the nonclassical type of CAH it is not always necessary to initiate GCs. When GCs are given in children, it is generally because the child has signs of hyperandrogenism, accelerated bone maturation or virilization in girls. In adults, men do not need treatment and women can be treated with oral contraceptive pills and antiandrogens. 12

Patients should also receive mineralocorticoid replacement. In patients with the classic type and the simple virilizing type, this replacement is done with fludrocortisone, but this medication should not be given to patients with the nonclassical presentation. It should be emphasized the importance of the correct dosage of these medications, since if given in excess they can lead to hypertension. 12

Finally, the patient’s compliance to the treatment is of utmost importance to obtain adequate results. Because CAH is a chronic condition, it is essential that the chosen drugs fit into the patients and their guardians routine. The possibility of a single daily dose of medication, such as GC with intermediary half-lives, has been proposed by many authors. 11

4.3 Newborn Screening

The newborn screening consists of a series of exams done during the first days of life, aiming for early diagnosis of various congenital and infectious diseases that can be cured or controlled. These pathologies can be asymptomatic during the neonatal period, but when specific management is initiated as soon as possible it can reduce or even eliminate the possible complications from the associated pathology. Included in the exams performed is the heel prick test, one
of the most important and should be done during the third and fifth day of life of the child.\footnote{13}

In Brazil the heel prick test, called \textit{Teste do Pezinho}, designed by the National Health Ministry includes tests for phenylketonuria, congenital hypothyroidism, sickle cell anemia and other hemoglobinopathies, cystic fibrosis, biotinidase deficiency and congenital adrenal hyperplasia. The exam consists of a small puncture on the newborn’s heel to obtain a dried blood sample on filter paper, this is the first sample. Afterwards, if a result is positive a confirmatory test is done with more specific methods using blood, urine or plasma, from the second sample. For CAH, the confirmatory test is done also using filter paper.\footnote{13}

The screening for CAH was one of the last to be developed, and because of this, was the last exam to be included in the \textit{Teste do Pezinho}. CAH diagnosis is based on the dosage of the hormone 17 OHP, since this biomarker is elevated 21-OHD. The first place to include 21-OHD in its screening program was Alaska, given the high incidence of this disease in the region.\footnote{13,14}

Currently, there are more than one type of test available for the neonatal screening for CAH, including radioimmunoassay, fluorimetry and mass spectrometry. The main biomarker used to detect CAH is 17-OHP, and mass spectrometry (a tool that separates ions to detect their mass-to-charge ratios quantitatively and qualitatively) is considered the gold standard. However, the value of 17-OHP has many variables that can compromise the diagnosis. Among these variables, the newborn’s level of stress, the immaturity of their organism and the concomitance with another pathology can generate false-positive results. On the other hand, the use of corticosteroids by pregnant women in the last weeks of pregnancy, decreases baseline levels of 17-OHP, which leads to false-negative results.\footnote{5,14}

The screening method is particularly effective for detecting the classic salt-wasting type of the disease, with almost all confirmed cases being detected with this assessment. On the contrary, the classic simple virilizing type, as well as the non-classical type, can generate unreliable results that can be more easily confused at the time of the examination, therefore, compromising the diagnosis and the specific adequate treatment, which can lead to death due to adrenal
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The main problems with the current test are related to the level of specificity of the cutoff point and the fact that 17-OHP suffers crossed influences with other steroids present within the plasma of the newborn. Beyond this, the screening is especially ineffective in diagnosing the non-classic form of the disease. In regards to the cutoff point, the challenge comes from the fact that lower values have a propensity for increased levels of false-negatives, despite covering a greater number of patients with the disease and its variations. On the other hand, when it is high, its sensitivity is markedly reduced, making it difficult to detect the pathology. With this in mind, technical improvements have been sought out to promote a screening with more reliable results for the diagnosis of CAH. Examples of these advancements include the association of the disease with mutation in the CYP21A2 gene, which has shown promising results in helping to clear doubtful cases and the consideration of the newborn's birth weight and gestational age to determine a cutoff point, is a measure that showed a cost-effective way to reduce false positives. With these methods, the medical community seeks to benefit children, reducing the number of complications and adjusting the treatment.5,13,14

4.4 Social Perspectives on Diagnosis through Newborn Screening for CAH

Newborn screening has changed the course of several diseases by allowing children to be treated before they even present clinical manifestations. For a disease to be included in a neonatal screening program, it must be considered frequent in the screening population, have high morbidity and mortality when not treated early, and must have a beneficial response to treatment. CAH fits all these requirements and therefore, screening for early diagnosis is essential for improved prognoses.5

Nevertheless, currently, the neonatal screening for CAH is still not universally accepted and is one of the most controversial diseases for inclusion in screening programs in several regions of the world. Although the cost-effectiveness of screening for CAH is still debated due to the factors elucidated above, it is worth noting that the advantages should be considered, especially in...
developing countries such as Brazil, where we observe a health system that is not fully consolidated and that still does not favor correct and rapid diagnosis.\textsuperscript{5}

Moreover, it is important to emphasize that it has been reported that screening for CAH is effective and necessary, because besides promoting a 74-86\% reduction in mortality in patients with CAH, it allows the family a notably less stressful experience than when the diagnosis is made from clinical manifestations. It is known that this disease causes changes that manifest themselves from the intrauterine period and that if treatment is not instituted early, continued exposure to excess androgens usually results in additional manifestations, including behavioral ones, which is why the diagnosis should be made early and treatment started without delay.\textsuperscript{5,15}

While it is important to emphasize that the discussion of sex and gender is not the focus of discussion in this study, it should be noted that sexual ambiguity in children with CAH may cause some parents distress. The human experience regarding sex and gender is complex and nuanced, and is beyond the mere appearance of the genitals. However, some research regarding the effects of androgens on the formation of a sexual identity hypothesize that embryos intensely subjected to androgens in prenatal life, such as patients with CAH, have a strong tendency to adopt a male identity later. Additionally, it has been shown that girls with CAH have a more male-typical gender behavior than those unaffected by the disease, while there was no difference in gender expression when comparing boys with and without CAH. Therefore, sexual ambiguity can cause a dilemma to parents, especially those faced with assigning a sex to the child, starting with the given name and can perpetuate itself in the way of educating and treating the child. Thus, it is possible to conclude that due to the complexity of psychological aspects evident in this disease, neonatal screening is extremely necessary and important.\textsuperscript{15,18}

5. Conclusion

Due to the evident psychological complexity of parents and children, early diagnosis of congenital adrenal hyperplasia is extremely important. The implementation of newborn screening is a milestone in pediatrics and genetics,
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already consolidated in developed countries and a reality in Brazil, that has the Teste do Pezinho in accordance with all international guidelines. Although Brazil does not have such a broad range of screened diseases as some of the richer countries, the tendency is that it continues to develop, with the inclusion of new pathologies. In this sense, it is important to expand the methodology and screening procedures for CAH, taking into consideration its consequences on patients, family members, and even health professionals who have daily contact with newborns and have to console the anxiety surrounding the health of these children. To this end, the ethical issues that accompany the science of molecular biology should be debated, but taking into consideration benefit to society.

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