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Creatine kinase in neonatal screening for Duchenne Muscular Dystrophy: an acceptability assessment

Creatina quinase na triagem neonatal para distrofia muscular de Duchenne: uma avaliação de aceitabilidad

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ABSTRACT

Objective: The present study evaluated the acceptance among parents of newborns to the creatine kinase (CK) test in the neonatal screening of Duchenne Muscular Dystrophy--DMD and raised possible barriers and elements that facilitate the acceptance of the test. **Methods:** The assessment of acceptance of the CK test for DMD screening was carried out through interviews, guided by a semi-structured script, with parents of newborns in the state of Mato Grosso, Brazil. **Results:** Six hundred and four parents participated in the research, only five being excluded for not meeting the eligibility criteria. The acceptance of screening among respondents was high (94.5%), surpassing that described in the retrieved literature. Long journeys to the collection site and the absence of information about the disease and the CK test can negatively influence parents regarding the performance of the test. The reduction in diagnostic delay seems to be a positive factor in the acceptance of screening. **Conclusions:** Non-mandatory neonatal screening for DMD using the CK test demonstrated high acceptance by the interviewed population; however, research has identified factors that can both motivate and discourage screening.

Keywords: Duchenne Muscular Dystrophy; neonatal screening; attitude.

RESUMO

Objetivo: O presente estudo avaliou a aceitação dos pais de recém-nascidos ao teste de creatina quinase (CK) na triagem neonatal da Distrofia Muscular de Duchenne-DMD e levantou possíveis barreiras e elementos que facilitam a aceitação do teste. **Métodos:** A avaliação da aceitação do teste de CK para triagem de DMD foi realizada por meio de entrevistas, guiadas por um roteiro semiestruturado, com pais de recém-nascidos do estado de Mato Grosso, Brasil. **Resultados:** Participaram da pesquisa 604 pais, sendo excluídos apenas cinco por não atenderem aos critérios de elegibilidade. A aceitação do rastreamento entre os entrevistados foi alta (94,5%), superando a descrita na literatura encontrada. Longos deslocamentos até o local de coleta e a ausência de informações sobre a doença e o teste de CK podem influenciar negativamente os pais quanto à realização do teste. A redução do atraso no diagnóstico parece ser um fator positivo na aceitação do rastreamento. **Conclusões:** A triagem neonatal não obrigatória para DMD pelo teste de CK demonstrou alta aceitação pela população entrevistada; no entanto, a pesquisa identificou fatores que podem motivar e desencorajar o rastreamento.

Palavras-chave: Distrofia Muscular de Duchenne; triagem neonatal; atitude.

Introduction

Duchenne Muscular Dystrophy (DMD) was first described in 1860 by the French neurologist Guillaume-Benjamin-Amand Duchenne[1]. It is a hereditary neuromuscular disease characterized by a recessive genetic mutation linked to the X chromosome that encodes dystrophin[2].

Dystrophin is a protein responsible for maintaining muscle structure and function, its loss causes degeneration of muscle fibers, resulting in progressive muscle weakness; this being the main pathological process of myopathic disorders such as DMD[3]. The first sign of this disease is the delay in ambulation that can be lost around the age of 8 to 12 years. In addition, at this stage the child may have cardiomyopathy and conduction abnormalities as well as bone fractures and scoliosis[4].

DMD has a worldwide prevalence of 19.8 per 100,000 live male births[5]. Two thirds of new cases are inherited from the mother, who carries the genetic information, the other third is the result of new mutations[6].

The absence of specific clinical symptoms favors a delay in the diagnosis of DMD, which is based on the clinical picture, family history, changes in serum levels of creatine kinase - CK, myopathic findings on electromyography and muscle biopsy that demonstrates absence or inactivity of dystrophin[7]. Confirmation of the disease is usually carried out by molecular diagnosis that are guided by the frequency of genetic events[8,9].

Several programs around the world have focused on the search and validation of screening tests that may favor the early diagnosis of DMD[10], such as neonatal screening based on the creatine kinase (CK) test. This biochemical marker appears elevated from 50 to 200 times above normal in children with the disease[10] and has good accuracy for this purpose with a specificity greater than or equal to 90% and a sensitivity of not less than 80%[8,9].

In Brazil, neonatal screening was incorporated into the public health system in 1992 under the name "Teste do Pezinho" with a mandatory character[12] and in 2011 the National Neonatal Screening Program was created[13]. However, screening for DMD is not included in this program.

The public health system of Mato Grosso, Brazil was in demand for the incorporation of the CK test in neonatal screening for DMD. Thus, the feasibility study of incorporating the aforementioned test required an assessment of its acceptability by the target audience, as recommended by the World Health Organization through the criteria of Wilson & Jungner[14].

A study conducted in the United States to assess the attitude of parents towards neonatal screening for genetic disorders, including Duchenne Muscular Dystrophy, pointed to an acceptance of 85%[15]. A Dutch study that investigated the opinion of prospective parents about neonatal screening for diseases that are incurable (treatable and untreatable) resulted in 73% acceptance[16]. In the state of Mato Grosso, parents' acceptance of the inclusion of the CK test for neonatal screening was unknown.

The objective of this study was to evaluate the acceptance of parents regarding a possible inclusion of the CK laboratory test for neonatal screening of DMD in the public health network in the State of Mato Grosso.

Material and Methods

To assess the acceptance of serum creatine kinase measurements in non-mandatory neonatal screening for DMD in the public health system in the State of Mato Grosso, Brazil, a descriptive, cross-sectional study was carried out with parents of newborns. The project was approved by the research ethics committee under number 35665220.4.0000.5164 and an informed consent form (ICF) was presented to potential participants explaining the research objectives, benefits and risks.

Sample

The composition of the sample was based on the records of newborns who participated in the National Neonatal Screening Program in the last 60 days and had their records captured by the Information System on Neonatal Screening – SISNEO, software used to automate that program.

To calculate the sample size, the equation recommended by MATINS (2001)[17] was adopted, which takes into account the sample size to estimate the proportion of a population of the event to be studied. An error of 4% was adopted, indicating that the distance between the sample estimate and the population parameter should not exceed this value and the propor-

tion to be estimated equal to .5; this value, for the fixed precision, requires a larger sample size, with a confidence level of 95%, which corresponds to the abscissa level of the standardized normal distribution.

To ensure the randomness of the sample, the randomization process was used with the help of the BioEstat software version 5.0. Parents were randomly selected by obtaining the value of the sample interval: the total number of parents responsible for the newborns divided by the sample size. Subsequently, a value between the number 1 and the sample interval is drawn; this being the first member to compose the sample.

Thus, the value of the sample interval was successively added to the number previously obtained, until completing the sample size.

Eligibility Criteria

Biological and/or non-biological parents of children up to 60 days old registered in the Information System on Neonatal Screening – SISNEO were considered eligible for the survey. On the other hand, parents of newborns, of any age, who presented aphonia, hearing impairment or difficulty understanding the Portuguese language to the point of making it impossible to approach via telephone were considered ineligible.

Recruitment of Research Participants

Potential research participants were approached via telephone by the researchers in an invitation format. The researcher, after identifying himself, briefly commented on the research and its objectives, asking if he would like to participate in it, behaving in such a way as not to interfere with the individual's decision-making autonomy.

From the interviews

The interviews were guided by a semi-structured script built on the following steps: (A) Programming of what would be measured with definition of the questions' themes. (B) Construction of the questions so that they were able to capture what was desired to be measured. (C) Decision on the wording and order of the questions, as well as the layout of the interview script. (D) Assessment of clarity, omission and ambivalence of the interview script through its testing with three parents of newborns.

The finalized and tested interview script consisted of an initial explanatory approach followed by questions including three criteria: acceptance of the test, access and accessibility, as well as a space to capture sociodemographic characteristics of respondents such as: gender; age; breed; income and schooling.

The introduction of the interview guide provided a brief explanation of what Duchenne Muscular Dystrophy – DMD is, as well as the advantages and disadvantages of a newborn being submitted to this screening; information from the screening test itself, emphasizing that performing the test requires peripheral blood collection.

The level of education and income assumed in the interview script were categorized according to the criteria of the Brazilian Institute of Geography and Statistics – IBGE[18].

For acceptance and access criteria, responses were collected based on the Likert scale[19]. As for the accessibility criterion, two open questions were asked in order to record the easiness and difficulties related to acceptance of the neonatal screening test for DMD. In the latter case, the respondent could point out more than one facility/difficulty.

The Likert scale corresponds to a collection of ordinal categories used to obtain people's opinion on a given topic. This scale allows for 5 levels of response that include acceptance, rejection and neutral position, also incorporating the emphasis with which acceptance and rejection are presented. Thus, instead of binary "agree" or "disagree" responses, the scale captures the strength of the respondent's agreement or belief[20,21,22]. The complete approach to the interview script is described in the Appendix A.

To mitigate possible harm and discomfort to the interviewees, the following measures were adopted: (a) the interviews were not recorded and were carried out in order to guarantee privacy and freedom to the interviewee not to answer questions that they considered embarrassing; (b) all researchers were trained for the method, being attentive to possible signs of discomfort on the part of the interviewee; (c) restriction of access to the interview script for researchers to ensure participant confidentiality; (d) guarantee of respect for habits and customs and religious, social, cultural, moral and ethical values expressed by the participants at the time of the interview.

Considered outcome

The percentage of parents of newborns who accept the newborn screening test for Duchenne Muscular Dystrophy – DMD was the primary outcome considered in the study. Possible facilitating factors and barriers reported by respondents were also considered.

Statistical analysis

The data collected in the research were stored in Microsoft Excel files and analyzed with the aid of the R application. The results were expressed using descriptive statistics through absolute and relative frequencies.

Results

Six hundred and five parents of newborns were eligible; however, only 600 interviews in this study since 05 parents had difficulties understanding the Portuguese language. Among the participants, there was a predominance of young individuals (51.2% aged between 20 and 29 years), mixed race (60.3%), female (87.3%), with income up to R$ 2038.00 (66.8%) and complete high school (39.7%). No difference was observed in relation to the sex of the neonates, as detailed in table 1.

Table 1. Profile of interviewed parents according to sociodemographic characteristics

Variable	Interval	Frequency (n)	Percentage (%)
Age	16 to 19 years	58	9.6
	20 to 29 years	307	51.2
	30 to 39 years	193	32.2
	≥ to 40 years	40	6.7
	Not declared	2	0.3
	Total	**600**	**100**
Race	White	125	20.9
	Black	86	14.3
	Brown	362	60.3
	Yellow	18	3
	Indigenous	2	0.3
	Not declared	7	1.2
	Total	**600**	**100**
Neonate's sex	Male	301	50.2
	Female	299	49.8
	Total	**600**	**100**
Interviewee's sex	Male	76	12.7
	Female	524	87.3
	Total	**600**	**100**
Income	R$ 2.038,00	401	66.8
	R$ 2.038,00 to R$ 4.156,00	158	26.3
	R$ 4.156,00 to R$ 10.390,00	30	5
	R$ 10.390,00 to R$ 20.780,00	1	0.2
	Not declared	10	1.7
	Total	**600**	**100**
Education level	No education or less than 1 year of study	1	0.2
	Incomplete elementary school	45	7.5
	Complete middle school education	44	7.3
	Incomplete high school	138	23
	Complete high school	238	39.8
	Incomplete higher education	50	8.3
	Complete higher education	65	10.8
	Postgraduate studies	11	1.8
	Not declared	8	1.3
	Total	**600**	**100**

Regarding the acceptance of the screening, it was observed that the vast majority of parents of newborns were in favor of the implementation of the CK test in the Unified Health System – SUS and only 1.7% were against the implementation (Table 02).

When asked about the place where the test was performed, for 55.8% of the parents, the place where the test was performed did not interfere with the availability to submit their child to screening. For 27%, this location is a determining factor, as detailed in table 3.

For the accessibility outcome, the most frequent facilitating factors were those related to information/dissemination (28.6%), place of testing (28.4%) and care for the newborn (13.6%) (See table 4).

Approximately half of the interviewees do not see any difficulty in submitting their children to a possible screening. Among those who reported some type of barrier, distance was the most frequently mentioned difficulty, as shown in Table 5.

A significant fraction of the parents of newborns (88.8%) were totally in favor of implementing the CK-MM test in the SUS. Lower percentages are observed among those whose positioning is indifferent, partially favorable and contrary to the implementation, according to data presented in table 6.

Discussion

Although Duchenne Muscular Dystrophy – DMD is a rare, incurable, little known disease that mainly affects males, the present study showed a high acceptance (94.5%) of the CK test for neonatal screening of DMD among the parents. This finding contrasts with the classic criteria by Wilson and Jungner[14] who consider that a screening program should not be considered in the absence of an accepted treatment for the screened individual. A similar acceptance was found in the study by Wood (2013) in the subgroup of parents of children affected by the disease (95.9% to 100%)[15]. The study by Plass (2010) carried out in the Netherlands with potential parents showed a lower acceptance, 73% of respondents showed a positive attitude towards the offer in the national program of neonatal screening for intractable diseases[16].

When questions regarding the place of collection were raised, in the present study, 55.8% of the parents would be willing to submit their children to screening regardless of the place where the test was performed. However, 23.8% pointed out concerns about the burden imposed by screening, preferring screening in places that require less effort from parents.

Table 2. Position of the parents of newborns regarding the implementation of the CK test in the SUS.

Positioning	Frequency (n)	Percentage (%)
I am totally in favor of implementing this test in the SUS	567	94.5
I am partially in favor of implementing this test in the SUS	15	2.5
I'm indifferent. For me it doesn't matter if the test is implemented or not.	8	1.3
I am totally against SUS implementing a test like this.	6	1.0
I am partially against SUS implementing a test like this.	4	0.7
Total	**600**	**100**

Table 3. Position of the interviewed parents regarding the location of the screening test.

Positioning	Frequency (n)	Percentage (%)
I would be totally willing to test my child regardless of where the test is performed.	335	55.8
I would submit my child to the test only if it was performed in the same place as the heel prick test ("Teste do Pezinho")	143	23.8
I'm indifferent	94	15.7
I wouldn't take my child to take the test if the test location was far from my house.	19	3.2
I would not take my child to take the test, regardless of where the test is performed.	9	1.5
Total	**600**	**100**

Table 4. Easiness for accepting the CK test according to the frequency with which they were reported by the research participants.

Easiness for accepting the CK test	Frequency (n)	Percentage (%)
Information about the disease and the test / Dissemination of the test during prenatal care, in basic health units and in the various television and social media.	173	28.6
Easily accessible place for exam collection	172	28.4
Care of the newborn (possibility of obtaining an earlier diagnosis of DMD; offering care to the child; preparing for the future; seeking a follow-up program after screening for identified DMD cases)	82	13.6
No formed opinion	46	7.6
Perform screening for DMD along with the heel prick test ("Teste do Pezinho")	40	6.6
Screening is free	23	3.8
Mandatory screening test	18	3.0
Free transport or transport provided by the public entity to the test site	18	3.0
Quality/ease in SUS care (reception, scheduling, reduction of queues, reduction in waiting time)	15	2.5
Punctuality in delivering results	6	1.0
Capillary blood collection for testing	4	0.7
Trained team to perform the exam collection	03	0.5
Screening recommended by the doctor	02	0.3
Extend the screening offer period	01	0.2
Offer a screening test that does not pose a risk to the child	01	0.2
Total	**604***	**100**

*4 interviewees indicated more than one facility.

Table 5. Difficulties in accepting the CK test according to the frequency of reporting by the interviewed parents.

Difficulties in accepting the CK test	Frequency (n)	Percentage (%)
Nothing would make it difficult to take the exam	298	49.7
Distance/need to move	152	25.3
	47	7.8
Difficulties in accessing the SUS (queue; bureaucracy; irregularity in care; lack of supplies; delay in results; difficulty in scheduling; shortage of pediatricians in the service network)	34	5.7
Lack of information about the disease and the importance of the test	23	3.8
Fear of hurting the baby/fear of the outcome	22	3.6
Cost to perform the test	07	1.2
Peripheral blood collection	06	1.0
Perform screening for DMD separate from the heel prick test	04	0.7
Leave work to use SUS services	03	0.5
Test a healthy baby	03	0.5
Perform the test after hospital discharge	01	0.2
Total	**600**	**100**

Table 6. Positioning of the parents of newborns regarding the implementation of the CK-MM test in the SUS.

Positioning	Frequency (n)	Percentage (%)
I am totally in favor of implementing this test in the SUS	533	88.9
I'm indifferent. For me it doesn't matter if the test is implemented or not.	30	5.0
I am partially in favor of implementing this test in the SUS	24	4.0
I am totally against SUS implementing a test like this.	11	1.8
I am partially against SUS implementing a test like this.	2	0.3
Total	**600**	**100**

With regard to accessibility, a quarter of respondents pointed to the need to travel to perform the screening as a barrier to access and almost a third reported that an easily accessible location would facilitate the acceptance of screening. These findings are similar to the review by Carlton J et al. (2021) which reveals, although the burden associated with screening varies between screening programs, the amount of effort required for parents to support the intervention can be considered onerous, since when screening can occur in settings that require little effort (within the hospital or at home), acceptance of screening increases. It also adds that the burden of attending appointments due to work commitments or transportation difficulties can lead to non-attendance[23].

The present study also revealed that 13.6% of parents see a benefit in screening as it allows an earlier diagnosis of DMD and thus, can offer care to the child seeking a follow-up program after screening. These results are in agreement with those reported by a study carried out in Chicago, USA, whose objective was to understand parents' attitudes, beliefs and concerns regarding neonatal screening for intractable diseases. The aforementioned study pointed out that parents believe that screening for DMD can reduce the delay in diagnosis and help families prepare for the future from an emotional and financial point of view. The argument that a long journey in search of the diagnosis can be avoided through the screening test was also the most reported justification in the study by Plass (2010)[16].

Of those interviewed, 29% approximately, pointed out that the dissemination of the disease (DMD) and the screening test during prenatal care, in basic health units and in the various television and social media could facilitate the acceptance of the test. This result, together with the high acceptance found in the research, may reveal the need to verify whether information regarding screening tests, including confirmatory genetic tests, is understandable and accessible to parents.

Today, neonatal screening for DMD in Brazil would be possible only by venipuncture of the newborn's peripheral blood, as the test is performed using the individual's plasma or serum. However, the national newborn screening program is performed by heel prick and parents of newborns have little or no experience with peripheral collection screening. This difficulty could be an unfavorable point for passing the screening test. However, this hypothesis was not confirmed in this research since the acceptance of the screening test by capillary puncture was lower than that by venipuncture.

Adherence to the National Neonatal Screening Program in the state of Mato Grosso was approximately 75% in the years 2018 to 2020, even though this program is mandatory[24,25]. Therefore, based on that data, it is possible that the high acceptance of the CK test for DMD screening in newborns found in this research does not correspond to a high adherence if it is effectively implemented in the public health system.

Conclusion

This study is part of a real-life assessment on the feasibility of implementing the creatine kinase – CK test as neonatal screening for Duchenne Muscular Dystrophy – DMD in the public health system of the state of Mato Grosso, Brazil.

Parental acceptance of the creatine kinase test in neonatal screening for Duchenne Muscular Dystrophy was high among respondents. Information about the disease and the test, easily accessible collection site and the possibility of early diagnosis of the disease were reported as facilitators for acceptance of the screening. On the other hand, distance was the most reported barrier to acceptance.

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Appendix A - Interview script – Neonatal Screening for Duchenne Muscular Dystrophy

Abordagem inicial

Estamos fazendo uma pesquisa de aceitação de um exame de laboratório chamado Creatina quinase – CK. Este exame fica alterado em distrofias musculares como a distrofia muscular de Duchenne - DMD.

• O que é distrofia muscular de Duchenne - DMD?
A distrofia muscular de Duchenne é uma doença genética mais comum nos meninos que se caracteriza, especialmente por fraqueza progressiva da musculatura esquelética, o que prejudica os movimentos. Normalmente os sinais e sintomas não aparecem antes dos 2 ou 3 anos de idade. Crianças com DMD podem andar mais tarde que outras crianças e evoluir para cadeira de rodas. A doença não tem cura e os indivíduos afetado têm uma sobrevida reduzida ("vivem menos").

• Qual a vantagem de um recém-nascido ser submetido a triagem para DMD?
Com o teste de triagem o diagnóstico da doença pode ser feito mais cedo e assim é possível retardar as alterações musculares com fisioterapia e outras terapias; além de cooperar com planejamentos futuros dos pais.

• Qual a desvantagem de submeter o recém-nascido ao teste de triagem?
Este exame não dá certeza de que a criança tem distrofia muscular. Entretanto, se der normal pode descartar a distrofia muscular. E ainda, embora existam alguns tratamentos a doença não tem cura.

• Como é feito o exame de triagem para DMD?
Assim como o teste do pezinho que testa se os recém-nascidos possuem algumas doenças genéticas para tratar o mais cedo possível, evitando problemas graves e até a morte; o exame de triagem levantaria a suspeita se a criança teria a DMD.

Atualmente o teste do pezinho faz triagem para doenças como: fenilcetonúria, hipotireoidismo congênito, doença falciforme e outras hemoglobinopatias, fibrose cística, hiperplasia adrenal congênita e deficiência de biotinidase.
No caso da triagem para DMD será necessário fazer a coleta de uma pequena quantidade de sangue na veia.
Gostaríamos de saber sua opinião.

Assim, imagine que o exame de CK para triagem neonatal de DMD seria de caráter opcional (NÃO OBRIGATÓRIO) e o SUS forneceria gratuitamente esse exame responda:

Pergunta aos pais

Critério: posicionamento quanto a uma possível implantação do teste

Qual sua opinião sobre o fornecimento desse teste de triagem no SUS?
( ) Sou totalmente a favor da implantação desse teste no SUS.
( ) Sou parcialmente a favor da implantação desse teste no SUS.
( ) Sou indiferente. Para mim tanto faz se o teste for ou não implantado.
( ) Sou totalmente contra o SUS implantar um teste como esse.
( ) Sou parcialmente contra o SUS implantar um teste como esse.

Critério: acesso

O local de realização do teste de triagem influenciaria sua decisão de levar seu filho (a) para fazer o teste? Escolha uma das alternativas abaixo:
( ) Estaria totalmente disposto a fazer o teste no meu filho (a) independentemente do local de realização do teste.
( ) Submeteria meu filho (a) ao teste apenas se este fosse realizado no mesmo local do teste do pezinho.
( ) Sou indiferente.
( ) Não levaria meu filho (a) para fazer o teste se seu local de realização fosse longe da minha casa.
( ) Não levaria meu filho (a) para fazer o teste, independentemente do local de realização do mesmo.

Critério: Acessibilidade

1. O que **facilitaria** você aceitar a realização do teste de triagem?

2. O que **dificultaria** você aceitar a realização do teste de triagem?

Critério: posicionamento quanto a uma possível implantação do teste caso ele fosse coletado no calcanhar.

Imaginando que houvesse disponibilidade desse teste de triagem para ser realizado em sangue seco (no papel de filtro) com coleta no pezinho (calcanhar)

Qual sua opinião sobre o fornecimento desse teste de triagem no SUS?

( ) Sou totalmente a favor da implantação desse teste no SUS.
( ) Sou parcialmente a favor da implantação desse teste no SUS.
( ) Sou indiferente. Para mim tanto faz se o teste for ou não implantado.
( ) Sou totalmente contra o SUS implantar um teste como esse.
( ) Sou parcialmente contra o SUS implantar um teste como esse.

Características dos respondedores

Sexo: ( ) Masculino ( )Feminino
Sexo do neonato:( ) Masculino ( )Feminino

Idade:

Raça:

Renda:
( ) até R$ 2038,00
( ) de R$ 2038,00 a R$ 4.156,00
( ) de R$4.156,00 a R$ 10.390,00
( ) de R$ 10.390,00 a R$ 20.780,00
( ) acima de R$ 20.780,00.

Grau de instrução:
( ) Sem instrução ou menos de 1 ano de estudo.
( ) Ensino fundamental incompleto
( ) Ensino fundamental completo
( ) Ensino médio incompleto
( ) Ensino médio completo
( ) Ensino superior incompleto
( ) Ensino superior completo
( ) Pós-graduação

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