

Desempenho de crianças com fenilcetonúria no Teste de *Screening* de Desenvolvimento Denver - II***

Performance of children with phenylketonuria in the Developmental Screening Test - Denver II

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Abstract

Background: phenylketonuria is an autosomal recessive disorder resulting from the mutation of a gene located in chromosome 12q22-24.1. Aim: to describe the performance of children with classic phenylketonuria, who were diagnosed and treated early, in the Development Screening Test Denver - II. Method: participants were 20 children with phenylketonuria, ranging in age from 3 and 6 years, and 10 children with typical language development, paired by gender, age and socioeconomic level to the research group. The plasmatic phenylalanine measure and the neurological, psychological and social information were gathered in the data base of the Neonatal Screening Programs for Metabolic disorder. Assessment consisted on the application of the Development Screening Test Denver II. A descriptive statistical analysis and the Mann Whitney test were used in order to characterize the tested skills. For the measurements of the plasmatic phenylalanine blood levels the values considered for analysis were: below 2mg/dL, above 4mg/dL, reference values between 2 and 4mg/dL, of all exams performed during the participants' lives; maximum and minimum values and values obtained on the day of the screening application. Results: comparison between the groups indicated statistically significant differences for the personal-social and language areas. Conclusion: children who were diagnosed and treated early for phenylketonuria present deficits in the personal-social and language areas. Also, even when receiving follow-up and undergoing treatment, these children presented difficulties in maintaining normal plasmatic phenylalanine levels.

Key Words: Phenylketonuria; Infantile Development; Language; Assesment.

Resumo

Tema: desempenho de crianças com PKU no Teste de *Screening* de Desenvolvimento Denver - II. Introdução: a fenilcetonúria é uma desordem autossômica recessiva resultante da mutação do gene localizado no cromossomo 12q22.24.1. Objetivo: caracterizar o desempenho de crianças com fenilcetonúria diagnosticadas e tratadas precocemente por meio do Teste de *Screening* de Desenvolvimento Denver II e dos níveis de fenilalanina sanguíneos. Método: participaram 20 crianças, dez com fenilcetonúria, diagnosticadas e tratadas desde o nascimento, de idade cronológica entre três a seis anos, e dez crianças do grupo típico, pareadas quanto ao sexo, idade e nível socioeconômico. Os níveis sanguíneos e as informações neurológicas, psicológicas e sociais foram obtidas no banco de dados do Programa de Triagem Neonatal para Erros Inatos do Metabolismo. A avaliação constou da aplicação do Teste de *Screening* de Desenvolvimento Denver-II. Utilizou-se estatística descritiva e aplicação do teste estatístico de *Mann Whitney* para a caracterização das habilidades. Para as medições dos níveis plasmáticos sanguíneos de fenilalanina considerou-se os valores abaixo de 2mg/dL, acima de 4mg/dL, os valores de referência entre 2 e 4mg/dL, de todos os exames realizados no decorrer da vida dos participantes, os valores mínimos e máximos e o valor obtido na época da avaliação fonoaudiológica. Resultado: A comparação entre os grupos foi estatisticamente significante nas áreas pessoal-social e de linguagem. Conclusão: crianças com fenilcetonúria diagnosticadas e tratadas precocemente apresentaram prejuízo nas áreas pessoal-social e de linguagem e, mesmo com o acompanhamento periódico, apresentaram dificuldades para manter os níveis de normalidade de fenilalanina, embora realizassem o tratamento recomendado.

Palavras-Chave: Fenilcetonúria; Desenvolvimento Infantil; Linguagem; Avaliação.

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Introduction

The Phenylketonuria (PKU) is a genetic disorder, resulting from the mutation of a gene located in chromosome 12q22-24.1 that codifies the phenylalanine hydroxylase enzyme, active in the liver and responsible for the transformation of the phenylalanine aminoacids (Phe) in tyrosine(1-5). The rise of the levels of phenylalanine in the blood(6) allows the passage in great amount of metabolites to the central nervous system (CNS), with toxic effect, causing cerebral diffuse damage involving dopaminergic pathways of the dorsolateral regions of the prefrontal cortex and alterations of the white substance (7-12). The recommended levels of phenylalanine during the treatment are still discussed in literature(1,5,6,12-16), however, there is unanimity regarding the rigorous control, mainly in first three years of life (1,6-12).

Untreated PKU children tend to present progressive cerebral function damage, developing many symptoms like: intellectual deficiency, global delay of the development, difficulties of learning, and autistic behavior(4,7,9,12-16). The intellectual deficiency is the most important sequelae of this illness which can be prevented with adequate treatment(2,6,12-15-18,19). Studies have observed alterations of the general development, of the executive functions, complications in the emotional development and low performance at school also in children with diagnosis and precocious beginning of treatment (7,9,10,20-27).

Considering the above, this study was delineated with the objective of characterizing the performance of children with PKU early diagnosed and treated by means of the development Screening Test- Denver II (TSDD-II) (28-30). and characterizing the levels of phenylalanine in blood.

Method

The study was approved by the Committee of Ethics in Research in Human Beings of the institution where the study was done (protocol number 116/2007). The ones legally responsible for the participants have signed the "Free and Illustrious Consent Term", following all the criteria of the resolution 196/96/ CONEP.

The selection and the characterization of the casuistics were done by means of analysis of handbooks of the data base of the Neonatal Screening Program selection for Innate Errors of the metabolism of Screening test of Associação dos Pais e amigos dos Excepcionais (APAE)- Bauru,

following the inclusion criteria:

- . possess classic phenylketonuria diagnosis;
- . be with age between 3 and 6 years;
- . accomplish treatment and attendance in Neonatal Screening Program, with appropriate adhesion, according to the Ministry of Health criteria(6), that is, no absence during treatment, periodic blood tests according to the age and proposed treatment;
- . present no other congenital or acquired alteration; genetic or neurological proven syndrome, which are not part of the phenylketonuria picture.

The casuistics was composed of twenty children. Ten of the group with phenylketonuria and ten of the control group, presenting typical development, same age, sex and social level. It is standed out that the age of the child of the control group should not exceed in three months of the age of his/her pair.

In the analysis of handbooks of the area of psychology and neurology, it was verified that none of the participants had the diagnosis of intellectual deficiency, but it was observed that the participants of the group with PKU 1,2,7 and 10 had been described with attention deficit and with difficulties to concentrate in the proposed activities. Participant 5 was also described as hyperactive. In the social area, all children were from low economic social level.

The Development Screening Test DENVER-II (TSDD-II) (28-30).

The TSDD- II(28-30), is a development scale that evaluates the following abilities: personal-social, language, fine motor-adaptive and gross motor. The results have been noted down following the manual of the instrument(30), considering the criteria below:

Attention (A): when the line of age is in the blue area of the bar of the test to be applied, and the child fails or refuses to do the proposed activity.

Refusal (R): when the child refuses to carry through the proposed activity

Delay (Atr): when the child does not show the abilities expected for the age band

Attention: it means that the child may be in the phase of acquiring the behavior, once the instrument was developed considering the "occurrence band". For example: if in the age band in question, between 75% and 90% of the children of this band carry through the behavior, and the target child does not, this means an attention and not a delay. If the child has more than two attentions in the same area, he/she will have to be reevaluated after familiar orientation and/or stimulation and, in these cases, it is considered that the child is presenting delay.

For the presentation of the referring results to the profile of the abilities of the development, descriptive statistics was used with values of relative frequency and application of the statistical test of Mann Whitney for the comparison of the average of non-parametric variables among two independent groups (level of significance= 0,05).

The following will be presented in percentages: the measurements of the plasmatic phenylalanine measure, below 2mg/dl, above 4mg/dl, the reference values between 2 and 4 mg/dL of all the examinations done during the life of the participants, according to normatives of the Program of neonatal selection for innate errors of the metabolism(6), the minimum and maximum values (mg/dl) and the value gotten in the blood examination at the time of the speech pathologist evaluation.

Resultados

Table 1 presents, in relative values (percentage), Attention (A), Refusal (R) and Delay (Atr) concerning the performance of the abilities personal-social (PS), motor fine-adaptive (MFA), language (Lgg) and gross motor (MG) of the TSDD for the group with PKU and the control group and the value of p gotten by means of the statistical test Mann Whitney.

Table 2 presents the measurements of the phenylalanine plasmatic blood levels (Phe) of the group with PKU, considering all measurements taken during the life of the participants, value ? 2mg/dL; between 2 and 4 mg/dL, ? 4mg/dL in percentage (%), value gotten in the day of the evaluation and the minimum and maximum values in mg/dL.

Table 2 presents the measurements of the plasmatic phenylalanine (Phe) of group PKU, taking all the measurements carried through in elapsing of the life of the participants, the values ? of 2mg/dL; mg/dL, ? 4mg/dL in percentage (%), the value gotten in the day of the evaluation and the minimum and maximum values in mg/dL enter 2 the 4.

TABLE 1. Percentages Attention (A), Refusal (R) and Delay (Atr) in the subtests of TSDD- II, for the group PKU and control group and value of p (Mann Whitney)

Performance Group							
TSDD- II	PKU			Control group			P value
	A	R	Atr	A	R	Atr	
PS	40%	0%	60%	10%	0%	0%	0,00*
MFA	50%	0%	10%	20%	0%	0%	0,05
Lgg	70%	0%	40%	10%	0%	0%	0,00*
MG	10%	0%	0%	10%	0%	0%	0,97

Legend: PS = Personal- social; MFA = Motor Fine Adaptive; Lgg = Language; MG = Gross motor; A = attention; R = refusal; Atr = delay; * = Statistically significant

TABLE 2. Percentages of the plasmatic levels, value gotten in the day of the evaluation and the minimum and maximum values.

P	?2 mg/dL (%)	2/4mg/dL (%)	?4mg/dL (%)	day of the test (mg/dL)	minimum value (mg/dL)	Maximum value (mg/dL)
1	31	24,2	44,8	11,	0,2	33,6
2	7,9	11,2	80,9	17,9	1,4	17,9
3	6,8	17,6	76,5	10,9	1,4	24
4	11,4	9,1	79,5	9,4	0,4	24,6
5	18,6	25,6	55,8	5,7	0,3	15,5
6	27,3	25,4	27,3	9,1	0,4	24
7	3,7	-	93,3	21	1,4	26,3
8	84,5	13,3	2,2	1,4	0,2	13,1
9	3,6	7,1	83,3	13,1	0,8	20
10	12,3	12,3	75,4	10	0,1	25,4

Discussion

The criterion that all the children with PKU would have to be in accompaniment and treatment with adequate adhesion is of extreme importance, therefore literature describes that children who delay the beginning of the diagnosis and do not take adequate treatment present risks for intellectual deficiency, global delays of the development and other manifestations, including neuropsychomotor delay, irritability, hyperactivity, behavior disorders and /or autistic behavior(2-4,7,11,12-14-16,18). However, even having the accompaniment and treatment initiated in precocious age, the following

are reported in literature: delays in the neuropsychomotor development, behavior disorders like hyperactivity, attention deficit, impulsiveness, not to stop seated, not to be able to concentrate oneself in the activities, sleep problems, irritability, school problems (5,7,13,14,17-22). No child presented autistic behavior which is expected mainly in the absence of the treatment or at the beginning of the delayed treatment(4). It should be highlighted that the children of the group with PKU, 1,2,5,7 and 10 in the psychological and neurological handbook were described as with lack of attention

and with difficulties to concentrate in the activities proposed and child 5 as also hyperactive, information confirmed in the evaluation with TSDD-II.

The comparison among the groups (Table 1) by means of the test of Mann Whitney was statistically significant in the personal-social and language areas. However in the motor fine adaptive area, the value obtained was 0,05. Although not being statistically significant, it corresponds accurately to the significance reference value, indicating caution in the interpretation of this ability, considering the size of the evaluated casuistic. Literature presents that individuals with low adhesion to the treatment or that are not able to keep the levels of phenylalanine in the recommended levels can present difficulties in the fine motor coordination(17). In the gross motor area, the value obtained was not statistically significant. Motor problems are frequently reported, mainly for those individuals who present delayed diagnosis of PKU(5,7,12). The findings of this study are compatible with some described in the literature in which it is reported that children with precocious diagnosis and treatment for PKU, tend not to present delay in the gross motor area(17,18).

The children of the group with PKU have presented worse performances in the personal-social areas, followed by the language and fine motor area, considering the category Delay. Studies have presented that children with PKU are of risk for alterations in the personal-social ability(2,3,5,7,13,17,20). In the personal-social ability, one observes the child's personal reactions in relation to the social environment that he/she lives, regarding the accomplishment, with independence, of tasks day by day, involving the organization of stimulus, the social performance, the perception of relations and the understanding of the context. It shouldn't be forgotten that this ability involves the development of the language, so that the child can decide problems, plan one's action and interact in the social environment, the language serves as mediator. So, alterations in the development or performance of the language, receptive and/or expressive, interfere in other fields of the development, mainly with the personal-social area, as well as this area interferes in the development and performance of the language(20).

The badly adaptative behaviors, like difficulty in keeping the attention in determined stimulations and hyperactivity also reflect in the performance of the child with consequences in the communicative abilities and of learning, as shows

literature(2,7,9,16-22,27).

Few studies have focused the language abilities specifically, but many studies have focused the damages of individuals with PKU, even with early treatment in the executive function(1,7,12,23-27). The executive function understand necessary abilities for the solution of problems, for instance, planning, operational memory, selective attention, flexibility and the inhibition and auto-regulation of the behavior(23). These functions are expressed complex behaviors that depend on the integrity of diverse cognitive processes, emotional motivational and volitive, contemplated in the personal-social activities and linguistic abilities(20).

Analyzing table 2, it is verified that the children with PKU, although fulfilling the treatment protocol(6), have presented the majority of the indices of phenylalanine out of the recommended values of reference.

The literature shows the influence in phenylalanine and tyrosine levels(1,2,5,7,10,11,16,17,19,23-25,27), that in excess, interferes in the cerebral protein synthesis, in the formation of the myelin, in the neurotransmitters, harming, mainly, the dopaminergic pathways of the regions of prefrontal and frontal cortex, being able to interfere in the integrative processing between these and cerebral distal regions, even in children with diagnosis and treatment of the PKU(2-10-20-27).

Influence of the biochemical disturbances in the functioning of the CNS has been studied, having as target the genetic disorder involving the gene 12q22.24.1 and mutations (3,4,5,11).

Although the majority of the participants of this study presented variations in the levels of phenylalanine sanguineous and delay in the personal-social areas, language and fine motor, it is not possible to affirm the accurate influence of these high levels of phenylalanine in the SNC, although literature demonstrates evidences in this relation(1-5,7-11,16-19,23-27).

In this study, this if must for the absence of examinations for images and genetic accompaniment, beyond other evaluations involving the effect of the free amino acid in the brain, as well as the susceptibility of each individual, how much the passage of amino acids for the barrier hemato- cephalic brain. However the precocious diagnosis associate to the accompaniment of the development of these children, with the dietary control and the plasmatic phenylalanine levels can assist for reduction of the deleterious effect of the PKU, being prevented alterations of the

development that will in general bring excellent consequences for its learning, influencing in the social integration, in the familiar and pertaining to school scope, contributing for improvement of the quality of life of these children. This is a subject little searched by the speech pathologist.

Conclusion

This study shows that even children with early diagnosis and treatment showed alteration in the abilities of personal-social and language and difficulty to keep the recommended plasmatic phenylalanine levels.

These alterations compromise its communication, intervening with its social integration and learning.

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