

PHENYLKETONURIA AND READING AND WRITING SKILLS

Fenilcetonúria e habilidades de leitura e escrita

Dionísia Aparecida Cusin Lamônica⁽¹⁾, Mariana Germano Gejão⁽²⁾,
Fernanda da Luz Anastácio-Pessan⁽²⁾

ABSTRACT

Purpose: to verify the performance of individuals with *phenylketonuria* diagnosed and treated early, at reading and writing performance and to correlate this with receptive vocabulary and Intellectual Quotient. **Methods:** participants were 17 individuals with chronological age between 7-14 years. All of them were attending public schools, from second to seventh grade. Data were collected from medical records on diagnosis, treatment, socioeconomic status, and scores of Intellectual Quotient and applied instruments: Peabody Picture Vocabulary Test and Academic Performance Test (subtest of writing and reading). Parents also answered questions about the context of everyday school life. Statistical analysis was inferential and applied the Pearson correlation test ($p \leq .05$). **Results:** analyzing the records it was found that no participant was able to maintain the levels of phenylalanine in normative indices lifelong; 29.41% were diagnosed with Attention Deficit Disorder and Hyperactivity, 41.17% had sleep problems and irritability and negativism 64.70%. At reading and writing subtests, 23.53% had scores consistent with their level of education, at average levels or above, 41.18% was classified as below average in the assessment of receptive vocabulary by Peabody Picture Vocabulary Test. It was found correlation between performance on tests of reading and writing and Intellectual Quotient scores and performance in receptive vocabulary test. **Conclusion:** although participants obtained normative scores in IQ, they presented difficulties in the performance at reading and writing subtests. Additional studies are needed to real understanding of the academic needs of individuals with phenylketonuria.

KEYWORDS: Phenylketonurias; Reading; Learning; Attention Deficit Disorder with Hyperactivity; Language

■ INTRODUCTION

Phenylketonuria (PKU) is an autosomal recessive disorder resulting from the mutation of a gene located in the chromosome 12q22-24.1^{1,2}. It is characterized by the partial or total deficiency of the hepatic enzyme phenylalanine hydroxylase (PAH) which, in excess, interferes in the cerebral protein synthesis and causes diffuse alterations in

the central nervous system (CNS)³. The incidence may vary from 1:2.600 to 1:26.000, with an average of 1:10.000⁴.

Phenylalanine (Phe) interferes in the development and in the functions of the CNS through different mechanisms. High levels of Phe in the brain can cause a decrease of neurotransmitters and hamper the connection between cells and/or result in demyelinating processes. Phe inhibits the collection of the precursor of the tyrosine and tryptophan amino acid in the brain, resulting in a decrease of dopamine and serotonin, causing a decrease of neurotransmitters, hampering the connection between cells and/or resulting in demyelinating processes⁵.

The Intellectual disability is the most important consequence of this disease, which can be avoided by an appropriate treatment with a restricted diet of Phe³. Other manifestations are described in the literature, such as hyperactivity, trembling, growth failures, autistic behaviors and/or conduct

⁽¹⁾ Departamento de Fonoaudiologia da Faculdade de Odontologia de Bauru da Universidade de São Paulo – FOB/USP, Bauru, SP, Brasil.

⁽²⁾ Faculdade de Odontologia de Bauru da Universidade de São Paulo – FOB/USP, Bauru, SP, Brasil.

Research carried out in the Speech Pathology / Audiology Department, Bauru School of Dentistry, University of São Paulo.

Research Source: CNPq

Conflito de interesses: inexistente

disorders⁵⁻⁹. Untreated children do not reach necessary initial development marks, sometimes showing a progressive compromise of brain functions, developing symptoms besides intellectual disability, behavioral disorders and autistic behavior, such as: irritability, learning disability, attention deficit, hyperactivity and convulsive seizures^{5,10,11}.

Normal physiological blood values of Phe should be kept between 2-4mg/dL, especially during the first years of life. The maintenance of levels up to 6 mg/dL in school age is acceptable, and so are levels under 10 mg/dl during the subsequent years of treatment¹², which should last for the individual's whole life

Children with early diagnosis and treatment may also present changes in their global development with significant consequences for physical, emotional, neuropsychomotor and linguistic development, with an interference in general learning and quality of life¹³. Even with the treatment, deficits in executive functions, a decrease of the information processing speed, hyperactivity and attention deficits reflecting on their academic performance may be also present¹⁴⁻²⁶.

The maintenance of the diet during life is a concern as PKU is a chronic disease^{1,5,6,14,21,25}. Studies have states that the lack of control and the diet discontinuity in adolescence and adulthood will bring disastrous consequences since these individuals can lose in school and work performance, interfering in the development of these areas^{19,25}. The difficulties in keeping the Phe levels under normative criteria also have a genetic explanation^{1,15,20,22}. There are children who, even with early diagnosis and treatment, with a rigorous diet control, cannot keep the Phe levels in the plasma recommended as normal standards.

Studies report changes in the white substance, which can be justified not only by the intracellular accumulation of metabolite effects generated by the PKU, but also by the influence of the PHA deficiency severity and the time of exposure to abnormal Phe levels. These changes reverberate on learning and neuropsychological functions^{20,26}. The predicted changes in the prefrontal and frontal cortex can be justified by the decrease of neurotransmitters, essential for the development of the cortical functions in these areas⁵, thus, resulting in deficits of the executive functions^{2,6,15-17,23,25}, with important repercussions for the academic development^{6,7,11,15,17,25}. The neural subtracts are not completely clarified yet and it is extremely relevant to know who the child is and the deleterious effects of the PKU.

Taking into account what has been stated, the objective of this study was to verify the reading and

writing performance of individuals with PKU, who were diagnosed and treated early.

■ METHODS

It is a cross-sectional prospective and exploratory study.

The project was approved by the Ethics Committee for Research on Humans at the Bauru School of Dentistry, University of São Paulo (FOB/USP), (Protocol 073/2010). All ethical procedures have been fulfilled according to the resolution 196/96 of CONEP (National Commission on Ethics in Research).

Procedures:

Analysis of institutional medical record for the purpose of collecting the following pieces of information: clinical history; age of diagnosis and start of treatment for PKU; attendance in appointments; test results for levels of blood Phe; results of medical, psychological (Wechsler Intelligence Scale for Children)²⁷ and social evaluations (Brazil Socioeconomic Classification Criteria – BSCC)²⁸, and interview with parents.

Speech evaluation focused on the reading and writing skills and academic performance using the following instruments:

- A questionnaire with the legal representatives consisting of questions on the context of school routine, for instance: Is your child doing well in school? Is the child keeping up with the class? Does the teacher have any complaint about the child learning? Does the child have behavior problems? Did the child receive any other medical diagnosis? Does the child attend speech or psychological therapeutic services?
- Peabody Picture Vocabulary Test (PPVT)²⁹ following the classification recommended by the instrument: evaluation of receptive vocabulary;
- Academic Performance Test – APT³⁰, following the classification recommended by the instrument: reading evaluation of 70 words (reading subtest) and writing evaluation of 34 words dictated and followed by supporting sentences, besides the writing of the participant own name (writing subtest).

Inferential statistical analysis was performed and the Pearson Correlation Coefficient Test (level of significance $p \leq 0.05$) was used to verify the correlation of IQ and receptive vocabulary with the performance in reading and writing tests.

Casuistry:

The selection of the casuistry was carried out by the analysis of the medical records of the database

from the Newborn Screening Program (NSP) of the Newborn Screening Laboratory at APAE, following the inclusion criteria below:

- Have the diagnosis of classical PKU obtained until the seventh day after birth;
- Be aged between seven and 14 and be a regularly enrolled student in public or private schools;
- Do monitoring and early treatment for PKU with adherence, according to the the national guidelines criteria, that is, without missing appointments, undergoing periodic examinations and treatment proposed by the NSP team;
- Do not exhibit other congenital or acquired alterations; proven genetic and / or neurological syndromes, which are not part of the specific context of PKU.

The study included 17 subjects who complied with all the inclusion criteria (64% males and 36% females). The chronological age ranged from 7 to 14 (an average of 10 years and two months). Regarding schooling, all subjects were public school 1st to 6th grade students.

■ RESULTS

Regarding the socioeconomic status (BSCC)²⁸, assessed by a social worker (medical record data), 23.52% were of B2 social class, 52.94% of C1 and 23.52% of C2 social class. All participants were users of the Unified Health System.

Although everyone had a classical PKU diagnosis obtained until the seventh day of birth, 23.53% began the treatment after the first month of life (medical record data). No participant managed to maintain all the Phe normative levels during follow-up (medical record data).

None of the participants presented a neuro-psychomotor development delay, nor changes of

physical growth; however, their legal representatives described 58.83% as distracted, 29.41% as hyperactive and distracted and 11.76% did not report complaints. The observations found in the medical records confirmed these indexes. It is worth mentioning that 29.41% of the cases were diagnosed as having Attention Deficit Hyperactivity Disorder (ADHD) by a neurologist of the PTN team. Sleep problems were reported by 41.17% of the representatives and irritability and negativity by 64.70%.

Regarding the school complaints, 58.83% of the legal representatives reported that their kids aren't keeping up with school and that they frequently receive complaints about their kids behavior and learning difficulties. From these, 41.17% are doing reinforcement in the opposite period. None of the patients undergo therapeutic treatment (psychology and/or speech therapy). In the questionnaire, the parents reported a difficulty in controlling their children's diet, especially after the child has entered school.

Table 1 presents the mean, median, minimum and maximum scores for the Chronological Age (CA) and Intellectual Quotient (IQ).

It was verified that none of the children presented an IQ below the normative indexes.

Table 2 presents the result of SPT, in the reading and writing tests as to the classification of the instrument (Low, Average, Upper average and Upper) regarding the N and percentages.

It was verified in the reading test that 76.47% presented a low classification, 17.65% average and 5.88% upper average. In the writing test, 76.47% presented a low classification, 5.88% average and 17.65% upper average. None of the children presented a superior performance than the expected for their school grade.

Table 1 – Values of Mean, Median, Minimum and Maximum scores for the Chronological Age and Intelligence Quotient

	Mean	Median	Minimum	Maximum
CA	122.18	121	84	168
IQ	88.94	89.2	70	118

CA: Chronological Age; IQ: Intelligence Quotient

Table 2 – Academic Performance Test Rank

Tests	Rank							
	Low		Average		Upper Average		Upper	
	N	%	N	%	N	%	N	%
Reading	13	76.47	3	17.65	1	5.88	0	0
Writing	13	76.47	1	5.88	3	17.65	0	0

Table 3 presents the results obtained by the participants in the classification of the TVIP (lower low, upper low, low average, average, high average, lower high, high, upper high) for N and percentages.

Scores average or above were verified for 58.52% and a lower to low average classification was verified for 41.18%.

Table 4 presents the statistical analysis, through the Pearson Correlation Coefficient, of the correlation of the performance found in the TVIP with the SPT reading and writing test and of the correlation of IQ with the performance in the SPT reading and writing test.

Table 3 – Peabody Picture Vocabulary Test Rank

PPVT Rank	N	%
Lower Low	3	17.65
Higher Low	1	5.88
Upper Low	3	17.65
Average	3	17.65
High Average	3	17.65
Lower High	2	11.76
High	1	5.88
Upper High	1	5.88

PPVT: Peabody Picture Vocabulary Test

Table 4 – Related Test between Peabody Picture Vocabulary Test and Reading and Writing; and between Intelligence Quotient and Reading and Writing.

	N	PCC	p-level
PPVT & Writing	17	0.52	0.032 *
PPVT & Reading	17	0.61	0.009 *
IQ & Writing	17	0.66	0.004 *
IQ & Reading	17	0.76	0.001 *

*: Statistically significant; PCC: Pearson Correlation Coefficient; IQ: Intelligence Quotient; PPVT: Peabody Picture Vocabulary Test

There was a significant correlation between the receptive vocabulary and the performance of participants in reading and writing. There was also a

significant correlation between the values obtained in the IQ test and scores obtained in reading and writing.

■ DISCUSSION

PKU is a chronic disease and the treatment must be done for the rest of one's life. Having said that, individuals with PKU and their families need to know about the expected consequences in case they don't have an appropriate attendance in the treatment, as, even having an early diagnosis and a proper treatment, the individuals can present sequelae if they aren't able to maintain the Phe levels under normative indexes²⁵.

The literature presents that early diagnosis of PKU is fundamental to prevent a mental disability^{5,7-10}. In fact, the participants of this study (Table 1) presented indexes of IQ ≥ 70 . Different studies have approached that mental disability is the main sequel, if the child doesn't receive treatment^{6,8,11}, but other variables must be taken into account because of the deleterious effects if there is no control over the Phe level during the individual's life.

Many studies reported that even when intellectual skills are in normative indexes, individuals with PKU can present a different performance than other children in the same school grade and also psychosocial problems^{2,6,15,16,18,20-23,25}. In this casuistry, complaints regarding the difficulties they have in school, behavior problems, sleep disorders, irritability and negativity were found. The results in the reading and writing tests (Table 2) obtained in this study corroborate with the literature data.

To be successful in school skills is a great concern to individuals with PKU. The literature has been supporting that even when the treatment is made, those individuals may present difficulties in school^{2,16}. The intellectual skills are usually within the average and there are academic difficulties, which can be related to ADHD, for executive function deficits and for a disability when it comes to how fast they process information⁶. It is necessary to verify which factors are fundamental for the learning process to happen, mainly when it is about the influence in the learning process of the executive functions, working memory, how fast they process an answer, inhibitory control, planning and organization of activities. Laboratory measures may not represent what happens on a daily basis, in school environment. Therefore, school tutoring is extremely relevant¹⁵.

Other symptoms that are very well described in literature, even in children with PKU who had an early diagnosis and treatment, refer to the ADHD^{5,8,14,18,22}. In this casuistry, family reported complaints about the attention deficit and the diagnosis of ADHD. This data were confirmed in the medical evaluations (analyzed records).

Some studies have related the attention deficit in individuals with PKU to metabolic changes that result from complex neurochemical mechanisms involved^{5,14-16,23}. There is a neurochemical instability, caused by the insufficient production of the dopamine and noradrenalin neurotransmitters, in the regions of the brain that are more related to the attention processing, with emotions and the wakefulness and sleep cycle (ascending reticular activating system, limbic system, frontal lobe, posterior and lower parietal region). When ADHD is associated with depression, changes also happen in the production of serotonin²³. Professionals must be very aware, because these events (lack of attention, hyperactivity or ADHD) can be part of the sequelae caused by the metabolic change; therefore fitting the PKU.

A variable, which usually appears related to the learning difficulties of individuals with PKU, refers to the control of serum levels of Phe, showing that the bigger the obedience to the diet and normal levels of Phe, the better the academic scores. Some studies carried out measurements of the levels of Phe to compare with the academic performance of these individuals^{8,13,16,18,23,25}. These studies concluded that normative levels of Phe favor the protection from biochemical attacks triggered by the PKU and it there seem to be differences when the Phe levels are high when SNC is still in the developing stage.

Such data is relevant, because, among kids with learning difficulties, the intelligence evaluation can give answers on which skills are harmed and, thus, help in the planning of teaching strategies. Besides these general indexes, there are many specific cognitive skills that are necessary to perform this instrument subtests, for example, attention skill, lexical knowledge, short term and long term memory, verbal comprehension and cognition. Using only IQ measures was a limitation of this study.

Despite of the relations between performance in reading and writing and the IQ scores, and the vocabulary performance, it is worthy to point out that the language development involves many factors that must be analyzed so that we can understand how this acquisition process develops. Generally speaking, these factors are about the general integrity of CNS, maturational process, sensory integrity, cognitive and intellectual skills, information processing or perceptual aspects, emotional factor and the environment influence.

We can't deny the environment influences in the acquisition and development of the spoken or written language. Better IQ performances can be related to the control of the Phe levels and to a better socio-economic level; therefore, it can also relate to the responsiveness of the parents and to other characteristics of the social-educational environment¹¹.

The participants of this study have a socioeconomically level related to the social classes B and C, they used the National Health Service (SUS), they were public schools students and despite the difficulties presented in school, they didn't perform therapeutic processes to keep up with such difficulties, despite the fact that 41,17% of them are doing school tutoring off class.

This study began with a survey for school problems with individuals with PKU. Studies focusing in specific skills such as memory, information processing, attention skills and executive functions are important since the literature points out to the occurrence of injuries in these processes, mainly for the individuals that cannot keep the Phe indexes under normative criteria^{2,6,15,16,23,25}.

The early diagnosis and treatment with dietary control was enough to prevent mental disability, once all the participants of this study had normative scores in the IQ tests. Additional studies are necessary to really comprehend the academic needs of individuals with PKU. Besides, the longitudinal follow-up, as for the literacy process and academic performance, are essential so that the deleterious effects of the metabolic change can be minimized.

In this casuistry, legal representatives said the treatment control was more difficult after the participants entered school because of the dietary. Studies^{19,25} also said that adolescence is a critical stage to keep up with the treatment using dietary control with low percentage of Phe. They informed this stage is particularly hard to control the diet as adolescents are more independent and spend more time in school.

■ CONCLUSION

Only 23.53% of the participants obtained scores compatible to their education level in average levels or above in reading and writing tests, though they all obtained normative scores in IQ tests. There was a correlation between the reading and writing tests performance and the IQ scores and the performance in the receptive vocabulary test.

■ ACKNOWLEDGMENT

We thank the staff of the Newborn Screening Laboratory at APAE and those who participated in this study.

RESUMO

Objetivo: verificar o desempenho de indivíduos com fenilcetonúria, diagnosticados e tratados precocemente, quanto à leitura e escrita e correlacionar este desempenho com vocabulário receptivo e Quociente Intelectual. **Métodos:** participaram 17 indivíduos com idade cronológica entre 7 e 14 anos. Todos cursavam escolas públicas do 2º ao 7º ano. Foram coletados dados dos prontuários sobre diagnóstico, tratamento, nível socioeconômico e escores do Quociente Intelectual e aplicados os instrumentos: Teste de Vocabulário por Imagem *Peabody* e Teste de Desempenho Escolar (subtestes de escrita e leitura). Os pais responderam questões sobre o contexto escolar. A análise estatística foi inferencial e foi aplicado o Teste de correlação de Pearson ($p \leq 0,05$). **Resultados:** analisando os prontuários verificou-se que nenhum participante conseguiu manter os níveis de fenilalanina em índices normativos ao longo da vida; 29,41% foram diagnosticados com Transtorno do Déficit de Atenção e Hiperatividade, 41,17% apresentavam problemas de sono e 64,70% irritabilidade e negativismo. Nos subtestes de leitura e escrita, 23,53% obtiveram escores compatíveis com seu grau de escolaridade, em níveis médios ou acima; 41,18% obtiveram classificação inferior à média baixa na avaliação do vocabulário receptivo por meio do Teste de Vocabulário por Imagem *Peabody*. Houve correlação entre o desempenho nas provas de leitura e escrita e os escores de quociente intelectual e o desempenho no teste de vocabulário receptivo. **Conclusão:** embora os participantes tenham obtido escores normativos em quociente intelectual, apresentaram dificuldades no desempenho dos subtestes de leitura e escrita. Estudos adicionais são necessários para a real compreensão das necessidades acadêmicas de indivíduos com fenilcetonúria.

DESCRITORES: Fenilcetonúrias; Leitura; Aprendizagem; Transtorno do Déficit de Atenção com Hiperatividade; Linguagem

■ REFERENCES

1. Bercovich D, Elimelech A, Zlotogora J, Korem S, Yardeni T, Gal N et al. Genotype-phenotype correlations analysis of mutations in the phenylalanine hydroxylase (PHA) gene. *J Hum Genet.* 2008;53:407-18.
2. Gentile JK, Ten Hoedt AE, Bosh AM. Psychosocial aspects of PKU: Hidden disabilities – A review. *Mol Genet Metab.* 2010;99:64-7.
3. Van Spronsen FJ, Hoeksma M, Reijngoud DJ. Brain dysfunction in phenylketonuria: Is phenylalanine toxicity the only possible cause? *J Inherit Metab Dis.* 2009;32:46-51.
4. Fidika A, Salewski C, Goldbeck L. Quality of life among parents of children with phenylketonuria (PKU). *Health Qual Life Outcomes.* 2013;28:11-54.
5. Moyle JJ, Fox AM, Arthur M, Bynevelt M, Burnett JR. Meta-Analysis of neuropsychological symptoms of adolescents and adults with PKU. *Neuropsychol Rev.* 2007;17(2):91-101.
6. Antshel KM. ADHD, learning, and academic performance in phenylketonuria. *Mol Genet Metab.* 2010;99:52-8.
7. Groot MJ, Hoeksma M, Blau N, Reijngoud DJ, Van Spronsen FJ. Pathogenesis of cognitive dysfunction in phenylketonuria: Review of hypotheses. *Mol Genet Metab.* 2010;99:86-9.
8. González MJ, Gutiérrez AP, Gassió R, Fusté ME, Vilaseca MA, Campistol J. Neurological complications and behavioral problems in patients with phenylketonuria in a Follow-up Unit. *Mol Genet Metab.* 2011;104:73-9.
9. Khemir S, El Asmi M, Sanhaji H, Feki M, Jemaa R, Tebib N et al. Phenylketonuria is still a major cause of mental retardation in Tunisia despite the possibility of treatment. *Clin Neurol Neurosurg.* 2011;113:727-30.
10. VanZutphen KH, Packman W, Sporri L, Needham MC, Morgan C, Weisiger K et al. Executive functioning in children and adolescents with phenylketonuria. *Clin Genet.* 2007;72:13-8.
11. Castro IPS, Borges JM, Chagas HA, Tiburcio J, Starling ALP, Aguiar MJP. Relationships between phenylalanine levels, intelligence and socioeconomic status of patients with phenylketonuria. *J.Pediatr.* 2012;88(4):353-5.
12. Brasil. Ministério da Saúde. Manual de normas técnicas e rotinas operacionais do programa nacional de triagem neonatal. Brasília: Ministério da Saúde; 2002 [acesso em 2012 jul]. Disponível http://bvsm.s.saude.gov.br/bvs/publicacoes/triagem_neonatal.pdf
13. Brumm VL, Bilder D, Waisbren SE. Psychiatric symptoms and disorders in phenylketonuria. *Mol Genet Metab.* 2010;99:59-63.
14. Thimm E, Schmidt LE, Heldt K, Spiekerkoetter U. Health-related quality of life in children and adolescents with phenylketonuria: unimpaired HRQoL in patients but feared school failure in parents. *J Inherit Metab Dis.* 2013.[Epub ahead of print].
15. Janzen D, Nguyen M. Beyond executive function: non-executive cognitive abilities in individuals with PKU. *Mol. Genet. Metab.* 2010;99:47-51.
16. Christ SE, Huijbregts SCJ, Sonnevile LMJ, White DA. Executive function in early-treated phenylketonuria: Profile and underlying mechanisms. *Mol Genet Metab.* 2010;99:22-32.
17. Sundermann B, Pfeleiderer B, Möller HE, Schwindt W, Weglage J, Lepsien J, Feldmann R. Tackling frontal lobe-related functions in PKU through functional brain imaging: a Stroop task in adult patients. *J Inherit Metab.* 2011;34(3):711-21.
18. Brumm VL, Bilder D, Waisbren SE. Psychiatric symptoms and disorders in phenylketonuria. *Mol Genet Metab.* 2010;99:59-63.
19. Campistol J, Gassió R, Artuch R, Vilaseca MA. Neurocognitive function in mild hyperphenylalaninemia. *Dev Med Child Neurol.* 2011;53:405-8.
20. Karlsgodt KH, Bachman P, Winkler AM, Bearden CE, Glahn DC. Genetic influence on the working memory circuitry: Behavior, structure, function and extensions to illness. *Behav Brain Resh.* 2011;225:610-22.
21. Van Spronsen FJ, Huijbregts SC, Bosch AM, Leuzzi V. Cognitive, neurophysiological, neurological and psychosocial outcomes in early-treated PKU-patients: a start toward standardized outcome measurement across development. *Mol Genet Metab.* 2011;104:45-51.
22. Van Spronsen FJ, Enns GM. Future treatment strategies in phenylketonuria. *Mol Genet Metab.* 2010;99:90-5.
23. Gassió R, Artuch R, Vilaseca MA, Fusté E, Colome R, Campistol J. Cognitive functions and the antioxidant system in phenylketonuria patients. *Neuropsychology.* 2008;22(4):426-43.
24. Malinowski P. Neural mechanisms of attentional control in mindfulness meditation. *Front Neurosci.* 2013;7(8):1-11.
25. Burton BK, Leviton L, Vespa H, Coon H, Longo N, Lundy BD et al. A diversified approach for PKU treatment: Routine screening yields high incidence of psychiatric distress in phenylketonuria clinics. *Mol Genet Metab.* 2013;108:8-12.
26. Anderson PK, Wood SJ, Francis DE, Coleman L, Anderson V, Boneh A. Are neuropsychological impairments in children with early-treated phenylketonuria (PKU) related to white matter abnormalities or elevated phenylalanine levels? *Dev Neuropsychol.* 2007;32(2):645-68.

27. Wechsler, D. Wechsler Intelligence Scale for Children – Third Edition (WISC-III): Manual. San Antonio: The Psychological Corporation; 1991.

28. Critério de Classificação socioeconômica Brasil. Associação Brasileira de Empresas de Pesquisa, 2012 [citado em 6jun 2011]. Disponível em: www.abed.org.

29. Dunn LM, Padila ER, Lugo DE, Dunn LM. Teste de Vocabulário por Imagens Peabody (Peabody Picture Vocabulary Test), adaptação hispanoamericana. Dunn Educational Services. Inc; 1986.

30. Stein LM. Teste de Desempenho Escolar: Manual para Aplicação e Interpretação. São Paulo: Casa do Psicólogo Livraria e Editora;1994.

Received on: August 20, 2013

Accepted on: May 07, 2014

Mailing address:

Dionisia Aparecida Cusim-Lamônica
Alameda Octávio Pinheiro Brisola nº 9-75, Vila
Universitária
Bauru – SP – Brsil
CEP: 17012-901
E-mail: dionelam@uol.com.br