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Characterization Of Patients Diagnosed With Phenylketonuria In The Neonatal Treatment Reference Service

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ABSTRACT

Phenylketonuria is an inborn error of autosomal recessive genetic metabolism, with partial or total deficiency of the hepatic enzyme phenylalanine hydroxylase, which converts L-phenylalanine into tyrosine, causing accumulation of phenylalanine at brain and serum levels, interfering with brain protein synthesis causing several damages. This study aimed to characterize patients diagnosed with phenylketonuria at the Neonatal Screening Reference Service from 2008 to 2017. Cross-sectional analytical study with a quantitative approach with retrospective data collection from medical records and databases. Data were grouped as baby gender, date of birth, time of birth and neonatal screening examination collection, type of delivery, gestational age and prenatal status, place of origin, phenylketonuria classification and coverage rate of neonatal screening. The sample consisted of 14 patients, where 64% were male, all mothers had prenatal care and the percentage of cesarean delivery prevailed with 57.2%. Of these 85.7% reside in other states of the country and on the classification of the type of phenylketonuria 64.3% have mild phenylketonuria, as for the coverage rate there was a drop in the number of collections in the reference service. This research contributed to characterize the patient diagnosed with phenylketonuria, which allows greater knowledge about the disease carriers, as well as favoring the reduction of irreversible sequels, expenses and morbidity.

Keywords: phenylketonuria. Newborn. Neonatal screening.

INTRODUCTION

Phenylketonuria is a disease of genetic origin of autosomal recessive character resulting from an inborn error of phenylketonuria metabolism. Also known as Phenylalanine Hydroxylase Deficiency (BROWN; LICHTER-KONECKI, 2016). It is a consequence of the mutation of the gene located on chromosome 12q22.24, which causes partial or total deficiency of the liver enzyme phenylalanine hydroxylase (PAH), which converts L-phenylalanine (Phe) to tyrosine (Tyr). This interferes with brain protein synthesis and causes extensive changes in the central nervous system causing serious cognitive and neurological deficits due to brain and serum phenylalanine accumulation (LAMÔNICA *et al.*, 2015).

Phenylketonuria or phenylpyruvic oligophrenia discovered by Asbjörn Folling, a physician, nutritional biochemist and professor of medicine at the University of Oslo, was initially identified and described as phenylpiruvic imbecilites. Folling identified in the urine of mentally retarded patients phenylpyruvic acid and phenylacetic acid, the most well-known form of all congenital aminoacidopathies, which occurs in about 10/100 000 live births (PANEQUE *et al*., 2013).

The diagnosis is made by the neonatal screening test popularly known as the little toe test that is performed within the first 48 hours from birth to the 5th day of birth. For the test five drops of blood are used (BRAZIL, 2016). The main objective of the neonatal screening program is early diagnosis and treatment initiation within the first 30 days of life (MARQUI, 2017).

Classical phenylketonuria has low enzymatic activity of phenylalanine hydroxylase, making it impossible to convert phenylalanine to tyrosine. Phenylalanine levels considered normal are higher than 20mg/dl (1200μM/l) and may still have higher values. Early diagnosis of classical phenylketonuria in neonatal screening is believed to favor appropriate treatment for patients and reduce possible complications. Complications may be less severe if values do not exceed 20mg/dl within phenylketonuria, being classified as mild with values greater than 10mg/dl (600μM/l) and enzyme activity below 1% (BONDY; ROSENBERG, 1974; MARTINS *et al.*, 2006).

Researchers have been analyzing normal values for the population and cutoff values from 2mg/dl to 4mg/dl have been acceptable. After altered neonatal screening cannot be confirmed diagnosis of phenylketonuria, the patient should be recalled for further collection for other tests (BRASIL, 2001).

A Hyperphenylalaninemia is a decrease in enzyme phenylalanine hydroxylase activity, as in transient hyperphenylalaninemia. Phenylalanine levels can be from 2 to 6mg/dl (120 to 360μM/l) (TRUNZO *et al*., 2016). Although this condition is persistent, it does not present any risk to the patient, since the elevation of plasma L-phenylalanine (Phe) levels is significantly slower than in classic phenylketonuria. In addition, substances such as phenylpyruvic acid and its derivatives are not produced in considerable quantities, even if they are not. In the absence of treatment, this implies that the most important clinical aspect is normal cognitive development (BONDY; ROSENBERG, 1974; MARTINS et al., 2006).

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Transient hyperphenylalaninemia presents a not uncommon occurrence among individuals with phenylketonuria, with Phenylalanine levels between 2 and 10mg / dl (120 to 600μM/l) and enzymatic activity higher than 5%, in which case there is a temporary immaturity in the phenylalanine hydroxylase enzyme may be decreased by a few weeks of life. A phenylalanine-restricted diet should be followed to prevent mental sequelae. Premature infants present this condition more frequently and may be associated with hypertyrosinemia, this situation may also occur in term newborns (BONDY; ROSENBERG, 1974; PINTO *et al.,* 2010; MARTINS *et al.,* 2006).

Maternal phenylketonuria, through studies, has recognized that high levels of altered phenylalanine and L-phenylalanine in women with phenylketonuria without dietary control are teratogenic for fetal development and may cause important sequelae such as microcephaly (73%), low birth weight (40%), cardiac anomalies (12%), developmental delay (92%), among other malformations (BONDY; ROSENBERG, 1974; MURPHY, 2015).

Otherwise, through strict dietary phenylalanine restriction initiated three months prior to conception until delivery for metabolic control during pregnancy, maternal phenylketonuria can be prevented with plasma L-phenylalanine levels below 360μmol / L (12mg / dl), the fetus will not present any type of malformation (MARTINS *et al*., 2006; MURPHY, 2015).

Deficient synthesis of the tetrahydrobiopterin cofactor (BH4) may cause hyperphenylalaninemia. This is due to the deficiency of the enzyme guanosine triphosphate cyclohydrolase. The cofactor performs the hydroxylation reactions of phenylalanine, tyrosine and tryptophan. The incidence reaches 2% of carriers with increased L-phenylalanine in most populations. Screening for BH4 cofactor deficiency should be performed in all newborns with persistent hyperphenylalaninemia because it is a treatment disorder with BH4 supplementation, neurotransmitter replacement therapy, and dietary change to regulate BH4 and concentration. of blood phenylalanine (REGIER; GREENE, 2017).

Screening and knowledge of phenylketonuria is essential for the diagnosis and early treatment of this pathology in order to improve the prognosis of these children. As well as preventing serious and irreversible sequelae, which represent a high cost for the child, the family and the health system (TEJADA-ORTIGOSA *et al*., 2019).

MATERIALS AND METHODS

This is a cross-sectional, analytical study with a quantitative approach with retrospective data collection. The research consisted of all patients with phenylketonuria diagnosed at the Neonatal Screening Reference Service of the State of Mato Grosso do Sul (Brazil) from 2008 to 2017. The patients were followed by the outpatient research Institute and Diagnostics of the Association of Parents and Friends of the Exceptional (IPED APAE). Patients with other metabolism-related diseases and those diagnosed with Phenylketonuria in other states of the country were excluded from the sample.

The variables studied were: baby gender, date of birth, time of birth, and data from the neonatal screening examination collection, type of delivery, gestational age and prenatal status, place of origin, phenylketonuria classification, and coverage rate neonatal screening in the years 2008 to 2017.

For statistical analysis of the data, a spreadsheet was prepared. The collected data was analyzed by the SPSS version 19.0 using percentage statistics.

The research was approved by the Research Ethics Committee Involving Human Beings of the Federal University of Mato Grosso do Sul under opinion number 3.354.977 and CAAE 13745619.4.0000.0021.

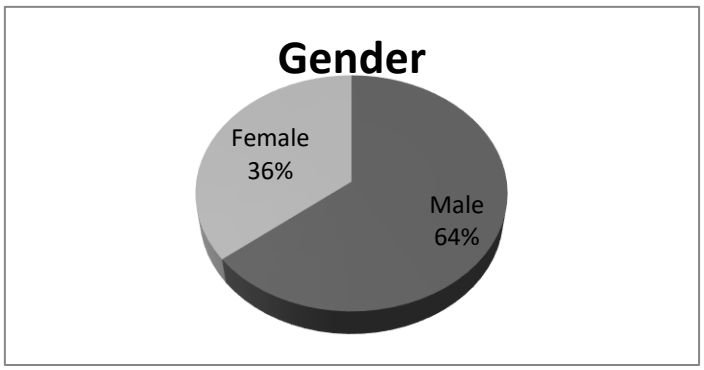
All stages of the study followed the recommendations of the National Health Council, through Resolution 466/2012, which presents the guidelines and regulatory standards for research involving human beings.

RESULTS AND DISCUSSION

From the system of the Neonatal Screening Reference Service of the State of Mato Grosso do Sul (Brazil), it was initially identified that 30 patients were being followed up at the outpatient clinic of the institution. Of these, 16 patients (53.3%) were excluded from the study because they did not meet the pre-established criteria. Of the 30 patients, (09) had their PKU diagnosed in another state and (07) of the patients had a date of birth outside the defined research period. Thus, the sample consisted of 14 individuals.

Regarding sociodemographic variables, there were a higher number of male cases. Freehaulf *et al*., (2013) found different results in the study where individuals diagnosed with phenylketonuria comprised 43 male and 33 female patients, with no significant difference between genders. This showed that patients diagnosed in the state of Mato Grosso do Sul have a higher incidence for males. See figure a below.

Figure a - Sex of Phenylketonuria patients diagnosed at the Neonatal Screening Reference Service of the State of Mato Grosso do Sul (Brazil) - 2008 to 2017.



Source: Prepared by the authors (2019).

Regarding the registration of the time of birth and the collection of the neonatal screening exam, some children presented only the record of the birth and other times of the collection of the foot test in medical records, and some cards were not correctly filled in conference.

According to the internal protocol of the referral service, exam collection cards are stored for up to 5 years and then discarded, making it impossible to know if they were correctly filled. It is of utmost importance the complete record with date and time of the information not to risk collecting the exam before the minimum recommended time.

Bernal and Eiroa (2017) in their research show that the test result can be false negative in 10% of cases if collected up to 24 hours of life and 2.4% between 24 and 48 hours, thus being undiagnosed, because that the newborn must have received protein feeding (breast milk) for at least 48 hours of life in order to present a phenylketonuria exam alteration.

All mothers of patients diagnosed with phenylketonuria (n = 14) performed prenatal care, but this fact does not guarantee that mothers were informed in prenatal about the importance of the foot test for their babies, being
hospital discharge postpartum without without the foot test. Mendes et al. (2017) states that misinformation negatively influences the early diagnosis of the disease as well as the initiation of treatment in a timely manner.

Figure b - Number and percentage of patients with phenylketonuria according to obstetric variables do neonatal screening service of the State of Mato Grosso do Sul (Brazil) - 2008 to 2017.

Variables	Nº.	%
Childbirth form		
Natural birth	6	42,8
Cesarean Birth	8	57,2
Gestational Age		
Preterm	1	7,2

Term	13	92,8
Post term	-	-
Prenatal		
Yes	14	100
Not	-	-

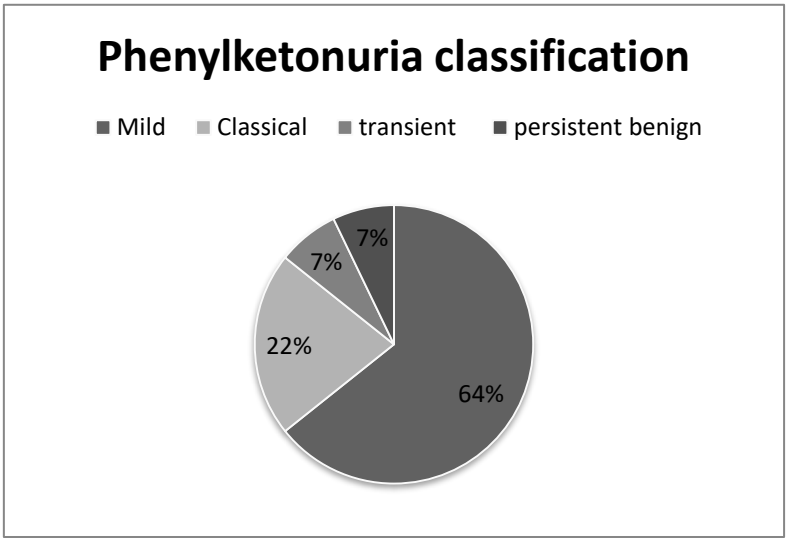
Source: Prepared by the authors (2019).

The sample patients live in 11 cities of the State of Mato Grosso do Sul (Brazil) as follows: Campo Grande, Três Lagoas, Paranhos, Itaquiraí, Rio Brilhante, Fatima do Sul, Dourados, Ivinhema, Naviraí, Mundo Novo and Bodoquena. Of the total sample of 14 patients with phenylketonuria, 14.4% were from the city of Paranhos.

Regarding the rate of occurrence of the disease in relation to the population of the state of (Brazil) whose population in 2017 was 2.713.147 inhabitants, we had an incidence of 1: 30.266 in the period of this research (2008 to 2017) where there were 423.727 live births and of these 14 were diagnosed with phenylketonuria.

According to the disease classification of the patients, 64.0% (n = 9) have mild phenylketonuria and have partial deficiency of the hepatic enzyme phenylalanine hydroxylase and with phenylalanine values greater than 10mg/dl requiring treatment. Complications are milder if rigorous treatment is performed throughout life (BONDY; ROSENBERG, 1974; MARTINS *et al.*, 2006). See figure c below.

Figure c - Phenylketonuria type classification presented by patients diagnosed at the Neonatal Screening Reference Service of the State of Mato Grosso do Sul (Brazil) - 2008 to 2017.

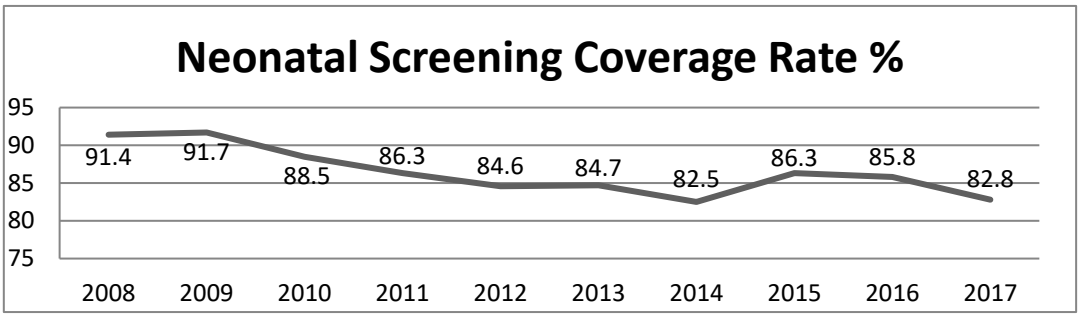


Source: Prepared by the authors (2019).

Analyzing the coverage rate for neonatal screening in 2008, the rate was 91.4% while in 2017 it was 82.8%, showing a decrease in the coverage rate. See figure d.

A study by Carvalho et al (2017) states that the low number of collections may be justified by the fact that the foot examination is being performed in private health institutions and the coverage rates of these institutions are not being computed by the institution state referral service. A more reliable coverage rate of the total state examinations would be possible if these fee amounts were passed on to the referral service.

Figure d - Neonatal screening coverage rate Neonatal Screening of the State of Mato Grosso do Sul (Brazil) - 2008 to 2017.



Dan et al (2001) say in their research that the disease may be underdiagnosed due to the low coverage rate and may be associated with lack of clinical suspicion of the condition for patients without test collection. In the country, the presence of many cases without phenylketonuria diagnosis seems to be a consensus, despite rare references (MIRA; MARQUEZ, 2000).

This research contributed to characterize the patient diagnosed with phenylketonuria, thus allowing greater knowledge about the pathology, its carriers and their individualities, and can reduce the abandonment of treatment, irreversible sequelae, morbidity and health and family expenses. .

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