Archives of Pediatrics and Neonatology
ISSN: 2638-5155
Volume 3, Issue 1, 2020, PP: 01-05

Phenylketonuria and the Interest of Introducing a Systematic Neonatal Screening: Case of Morocco

Chaimae khairoun*, Hajar Rhouda, Ghizlane Zouiri, Sanae Moussaoui, Kriouile Yamna

Rabat Children's Hospital, Clinic of Neuropediatric and Metabolic Diseases, Faculty of Medicine and Pharmacy, Mohamed V University, Rabat, Morocco.

Chaimaekhairoun1@gmail.com

***Corresponding Author:** Dr. Chaimae Khairoun, Pediatric Resident, Clinic of Neuropediatric and Metabolic Diseases Department of Rabat Children's Hospital, Faculty of Medicine and Pharmacy of Rabat, Morocco.*

Abstract

Phenylketonuria is a serious metabolic disease caused by a defect in the enzyme that breaks down an amino acid. Untreated, it can lead to behavioural problems and mental disorders. Our work concerns a prospective study of 23 cases, of children with phenylketonuria, diagnosed late at the stage of psychomotor retardation and followed in the neuro-paediatrics department of University Health Centre of Rabat, Morocco, over a period of 11 years from January 2008 until November 2019. The interest of our work is to draw public health attention to the interest of the introduction of systematic neonatal screening for phenylketonuria in developing countries.

Introduction

Phenylketonuria, also called PKU, is an inherited disorder linked to a defect in the hepatic phenylalanine hydroxylase activity. This enzyme converts an amino acid, called phenylalanine (PHE) to tyrosine [1, 2]. More rarely, but much more serious, this disease can be caused by a deficiency of the PAH cofactor called tetrahydrobiopterin (BH4 or THB). Blocking this metabolic pathway causes a dangerous build-up of PHE in the blood, thing that can eventually lead to serious health problems. The treatment is essentially preventive, based on a diet allowing controlled distribution of PHE [2]. We report a series of children with phenylketonuria diagnosed at the mental retardation stage. The aim of which is to draw the attention of Moroccan public health officials to the value of introducing a systematic neonatal screening in Morocco.

Materials and Methods

Our work concerns a prospective study of 23 cases of children with phenylketonuria, diagnosed late at the stage of psychomotor retardation and followed in the Paediatric Neurology department of the University Hospital of Rabat IBN SINA, Morocco over a period of 11 years from January 2008 until November 2019.

Results

For the purposes of this study, we included all children under the age of 17, admitted to the Paediatric Neurology department of RABAT for neurological and/or psychomotor problems with a high level of phenylalanine.

An operating sheet has been drawn up including identity, age at the diagnosis, sex, reasons for consultation, inbreeding, the presence of similar cases in the family, the level of phenylalanine, patient adherence and evolution.

We excluded from our study 2 children diagnosed during the first week of life given the presence of similar cases in siblings. All in all, 23 cases were identified during an 11-year period from 2008 to 2019. The age at the time of diagnosis was between 14 months and 16 and half years with an average age of 5 years and 9 months. For the sex of our patients, we have a female predominance with a sex ratio of 0.43 (7 boys and 16 girls).

Through our series, we found that the 23 patients consulted for different reasons, dominated by the psychomotor retardation, which represents 48% as shown in the figure below:

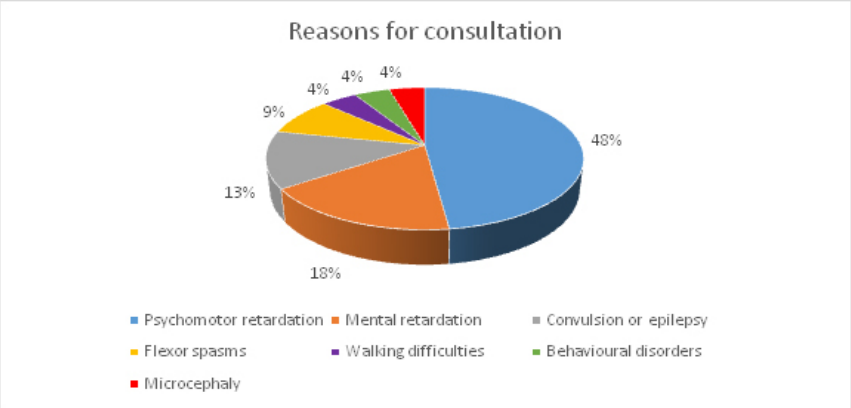

Fig1. *Reasons for consultation of the 23 patients of the study*

We found that 39% of our patients had similar cases in the family (siblings represented 17.4%). These results are explained by the consanguinity found in 35% of cases. The clinical symptomatology is dominated by cognitive (20%) and language disorders (17.78%) as shown in the following table (Table 1):

Table 1. *The clinical symptomatology of the studied patients*

Symptomatology	Percentage
Cognitive disorders	20%
Language disorders	17,78%
Autism spectrum disorder	15,55%
Microcephaly	11,11%
Delayed walking	6,67%
Behavioural issues	6,67%
Abnormal movements	6,67%
Psychomotor delay	4,44%
Convulsions	4,44%
Hyperactivity	2,22%
Spasms	2,22%
Failure to thrive	2,22%

Hyper-phenylalaninaemia was found in all patients with an interval of 75 to 1947 µmol/l and an average of 1184.6 µmol/l. A diet-based treatment devoid of phenylalanine was initiated in all patients but with poor therapeutic adherence.

The evolution of our patients was marked by a moderate improvement in cognitive disorders, gait disturbance and social contact. We have noticed the disappearance of seizures and spasms in all our patients. We were able to keep an average phenylalanine figure estimated at 452 µmol/L.

Discussion

Phenylketonuria (PKU) is a metabolic disease caused by the accumulation of non-catabolized Phenylalanine, which is harmful to the neuronal development of the newborn.

A systematic and early neonatal screening, at 3 days of life, has been established in France since 1968. If the disorder is detected, a restrictive diet of Phenylalanine is systematically adopted. This screening, originally discovered by Robert Guthrie in 1963, has literary changed the natural history of the disease.

Globally, the prevalence is estimated at 1/4000 live births in Turkey, explained by the high rate of consanguineous marriage among this population. This rate is estimated at 1/100,000 in Africa and 1/143,000 in Japan [3]. In the United States, this prevalence rises to 1 in 15,000. Itis estimated at a maximum of 1/10,000 live births in Europe, with higher values in certain countries (such as Northern Ireland and Italy) as shown in the table above:

Table 2. *The prevalence of Phenylketonuria by countries*

Country	England	Germany	Spain	Northern Ireland	Italy
Prevalence (screened/diagnosed)	1/10 000	1/8 553	1/6 532	1/4 500	1/3 654

In France, the prevalence of PKU is under control thanks to the implementation of systematic neonatal screening as stated above. Although the estimated number of births in 2013 was at 845,000, the number of newborns screened was 829,570, thing that helped to detect 45 PKU patients. [4]

In Morocco, there are currently no national data on the prevalence of PKU. The clinical picture of untreated children is dominated by brain development disorders such as microcephaly, epilepsy, severe intellectual impairment and behavioural problems. Other disorders have been described such as eczema, hypopigmentation of both skin and hair [5]. Tremor, paraplegia or hemiplegia may appear later in life [6,7].

When PKU is untreated or treated late, sick persons may develop behavioural or psychiatric problems (such as depression, anxiety and phobias) during their third or fourth decade [8]. In our series, we found that 48% of patients had a psychomotor retardation, 18% with mental retardation, 20% with cognitive impairment, and 15.5% with autism spectrum disorder. By analysing these results, Moroccan public health professionals must to take action so that the screening for phenylketonuria became systematic from the neonatal period before the onset of irreversible neurological disorders.

In 1954 (20 years after the discovery of the disease), Professor Horst Bickel spoke of the establishment of a diet low in Phenylalanine. This PKU treatment consists of a drastic reduction of whole food protein sources. This therapeutic approach should ideally be started in the first or second week of life in order to effectively protect the development of the central nervous system from the toxic effects of hyper-phenylalaninaemia[9-11]. The aim is to maintain a serum phenylalanine level between 2 to 5 mg / dl (120 to 360 µmol / l) during the first 10 to 12 years of life. [12]

Maintaining this appropriate diet after the age of 10 may be considered but with differences in recommendations according to each country as shown in Table 3 [13]:

Table 3: *Recommended Phenylalaninaemia according to age in Europe and the United States. [13]*

Age	Phenylalanine in µmol/L			
	United kingdom	Germany	France	United States
Birth	> 400	> 600	> 600	> 600
Until 10 years	120-360	40-240	120-360	120-360
10-12 years	< 480	< 600	< 900	120-360
12-20 years	< 480	< 600	< 900	120-600
>20 years	< 700	< 1200	<900-1200	120-900
Pregnancy				120-360

In our case, the diet was adopted by all the patients but with poor therapeutic compliance, explained by the low socio-economic level, the expensive cost of dietetic products not available in Morocco and the lack of treatment or state subsidy. This explains the moderate improvement of our patients.

New drugs, not yet marketed in Morocco, have been introduced in developed countries. Among these drugs, we cite:

- Sapropterin dihydrochloride, which decreases the risk due to serum hyper-phenylalaninemia either by compensating for enzyme deficiency (phenylalanine hydroxylase), or insufficient activity of the cofactor thereof (BH4). [14]
- Glycomacropeptide, which is a protein derived from cheese, rich in specific essential amino acids but naturally deprived of phenylalanine [15]. It allows normal growth of the young patient, with improved metabolic controls and a significant drop of Phenylalanine concentrations in both blood and brain[16].

- Supplementation with neutral amino acids LNAA, which reduce the concentration of PHE in the brain despite the constantly elevated serum PHE concentrations in competition with this transporter [17, 18]. Its effectiveness has been demonstrated by a decrease in the slowing down of the activity of the electroencephalogram, which is observed during prolonged exposure of the brain to high concentrations of Phenylalanine[19].

Conclusion

Phenylketonuria is a serious metabolic pathology responsible for a great handicap. The establishment of a neonatal screening system is the only reliable preventive means to avoid irreversible neurological complications. Treatment with a low phenylalanine diet is effective. However, the high cost of dietetic products and the limited number of associations that can help this population represent the main obstacles for better management of this pathology in the Moroccan context.

References

[1] Feillet F. Phénylcétonurie. La presse médicale. 2006;35(3):502-8.

[2] Abadie V. Devenir à l'âge adulte du nouveau-né atteint de phénylcétonurie. Archives de pédiatrie. 2007; 6(14): 607-9.

[3] Blau N, van Spronsen FJ, Levy HL. Phenylketonuria. Lancet (London, England). 2010; 376(9750): 1417-27.

[4] Sarles J. Place du pédiatre dans le dépistage néonatal. Archives de Pédiatrie. 2015; 22(12): 1318-20.

[5] Hassel CW, Jr., Brunsting LA. Phenylpyruvic oligophrenia; an evaluation of the light-sensitive and pigmentary characteristics of seventeen patients. AMA archives of dermatology. 1959; 79(4): 458-65.

[6] Pietz J. Neurological aspects of adult phenyl ketonuria. Current opinion in neurology. 1998; 11(6): 679-88.

[7] Perez-Duenas B, Valls-Sole J, Fernandez-Alvarez E, Conill J, Vilaseca MA, Artuch R, et al. Characterization of tremor in phenylketonuric patients. Journal of neurology. 2005; 252(11): 1328-34.

[8] Hanley WB. Adult phenylketonuria. The American journal of medicine. 2004; 117(8): 590-5.

[9] De Roche K, Welsh M. Twenty-five years of research on neurocognitive outcomes in early-treated phenylketonuria: intelligence and executive function. Developmental neuro psychology. 2008; 33(4): 474-504.

[10] Stemerdink BA, Kalverboer AF, van der Meere JJ, van der Molen MW, Huisman J, de Jong LWA, et al. Behaviour and school achievement in patients with early and continuously treated phenylketonuria. Journal of Inherited Metabolic Disease. 2000; 23(6): 548-62.

[11] Diamond A, Prevor MB, Callender G, Druin DP. Prefrontal cortex cognitive deficits in children treated early and continuously for PKU. Monographs of the Society for Research in Child Development. 1997; 62(4): i-v, 1-208.

[12] Phenylketonuria (PKU): screening and management. NIH consensus statement. 2000; 17(3): 1-33.

[13] MacLeod EL, Ney DM. Prise en charge nutri tionnelle de la phénylcétonurie. Annales Nestlé (Ed française). 2010; 68(2): 60-71.

[14] Manus J-M. Phénylcétonurie: le premier traitement jamais inventé. Revue Francophone des Laboratoires. 2010; 420(2010): 16.

[15] Laclair CE, Ney DM, MacLeod EL, Etzel MR. Purification and use of glycomacropeptide for nutritional management of phenylketonuria. Journal of food science. 2009; 74(4): E199-206.

[16] Ney DM, Hull AK, van Calcar SC, Liu X, Etzel MR. Dietary Glycomacropeptide Supports Growth and Reduces the Concentrations of Phenylalanine in Plasma and Brain in a Murine Model of Phenylketonuria. The Journal of Nutrition. 2008; 138(2): 316-22.

[17] Pietz J, Kreis R, Rupp A, Mayatepek E, Rating D, Boesch C, et al. Large neutral amino acids block

phenylalanine transport into brain tissue in patients with phenylketonuria. The Journal of clinical investigation. 1999; 103(8): 1169-78.

[18] Moats RA, Moseley KD, Koch R, Nelson M, Jr. Brain phenylalanine concentrations in phenylketonuria: research and treatment of adults. Pediatrics. 2003; 112(6 Pt 2): 1575-9.

[19] Pietz J, Kreis R, Rupp A, Mayatepek E, Rating D, Boesch C, et al. Large neutral amino acids block phenylalanine transport into brain tissue in patients with phenylketonuria. The Journal of clinical investigation. 1999; 103(8): 1169-78.

Citation: **Chaimae khairoun, Hajar Rhouda, Ghizlane Zouiri, et. al.** *Phenylketonuria and the Interest of Introducing a Systematic Neonatal Screening: Case of Morocco. Archives of Pediatrics and Neonatology. 2020; 3(1): 01-05.*