REVIEW ARTICLE

CONTENTS

Phenylketonuria – newborn screening as a health protection in society

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ABSTRACT

Aim: Phenylketonuria is the most prevalent inherited metabolic disorder. Early detection and prompt treatment can prevent serious neurological consequences. This has become possible thanks to the implementation of newborn screening programmes. The objective of this review is to provide readers with a comprehensive understanding of the phenylketonuria and the role that neonatal screening plays in the protection of public health.

Materials and Methods: A review of the literature was conducted using the PubMed database, with the search period encompassing the most recently published scientific sources. Analysis of the literature. This article presents phenylketonuria as an example of an inherited metabolic disorder, outlines the treatment options, and discusses the potential implications of hyperphenylalaninemia. Furthermore, it also delineates the various aspects of health that are influenced by newborn screening.

Conclusions: Phenylketonuria represents a significant health problem in the population. The development of screening tests has transformed healthcare, including improvements in quality of life, prognosis, and reductions in the number of comorbidities in patients. It is essential to disseminate knowledge among the society about the importance of newborn screening tests in order to enhance awareness and prevent refusal to participate.

KEY WORDS: phenylketonuria, inherited metabolic disorders, newborn screening, health protection

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INTRODUCTION

Phenylketonuria (PKU) is an autosomal recessive error of amino acid metabolism, that affects about 1 in 10000 newborns in Europe [1]. The majority of cases are caused by a mutation in the phenylalanine hydroxylase (PAH) gene, which results in the absence or reduced activity of PAH, the liver's enzyme that catalyses the conversion of phenylalanine to tyrosine. Abnormalities in the enzyme's cofactor, tetrahydrobiopterin (BH4), are responsible for a small number of cases [2]. Table 1 illustrates the fundamental metabolic phenotypes in relation to blood phenylalanine (Phe) concentrations. The most common and severe phenotype is classical PKU [3]. High levels of Phe cross the blood-brain barrier and accumulate in the brain. In addition, lower levels of tyrosine lead to a reduced synthesis of neurotransmitters such as dopamine and noradrenaline [4]. The clinical manifestations include severe mental retardation, epilepsy, neurocognitive deficits and behavioural issues. Patients also experience a musty smell, hypopigmentation of the skin, hair, irises, and eczema [5]. It is crucial to highlight that these symptoms can be prevented through the immediate initiation of treatment [6]. This is made possible by the early diagnosis provided by newborn screening programmes.

AIM

The aim of the review is to increase awareness among the population about phenylketonuria and the importance of newborn screening. It emphasizes how their development has significantly enhanced the quality of life and prognosis of patients. The purpose is to demonstrate that participation in neonatal screening is a crucial aspect of health protection.

MATERIALS AND METHODS

A review of the literature was conducted using the PubMed database. In order to identify the most recent scientific sources, the results were limited to a period between 2015 and 2024. The search terms were formu-

Table 1. Metabolic phenotypes and corresponding pre-treatment blood Phe concentrations [3].

Metabolic phenotypes	Pre-treatment blood Phe concentrations
Classical PKU (cPKU)	> 1,200 µmol/L
Mild PKU (mPKU)	600–1,200 µmol/L
Mild hyperphenylalaninemia (MHP)	120–600 µmol/L

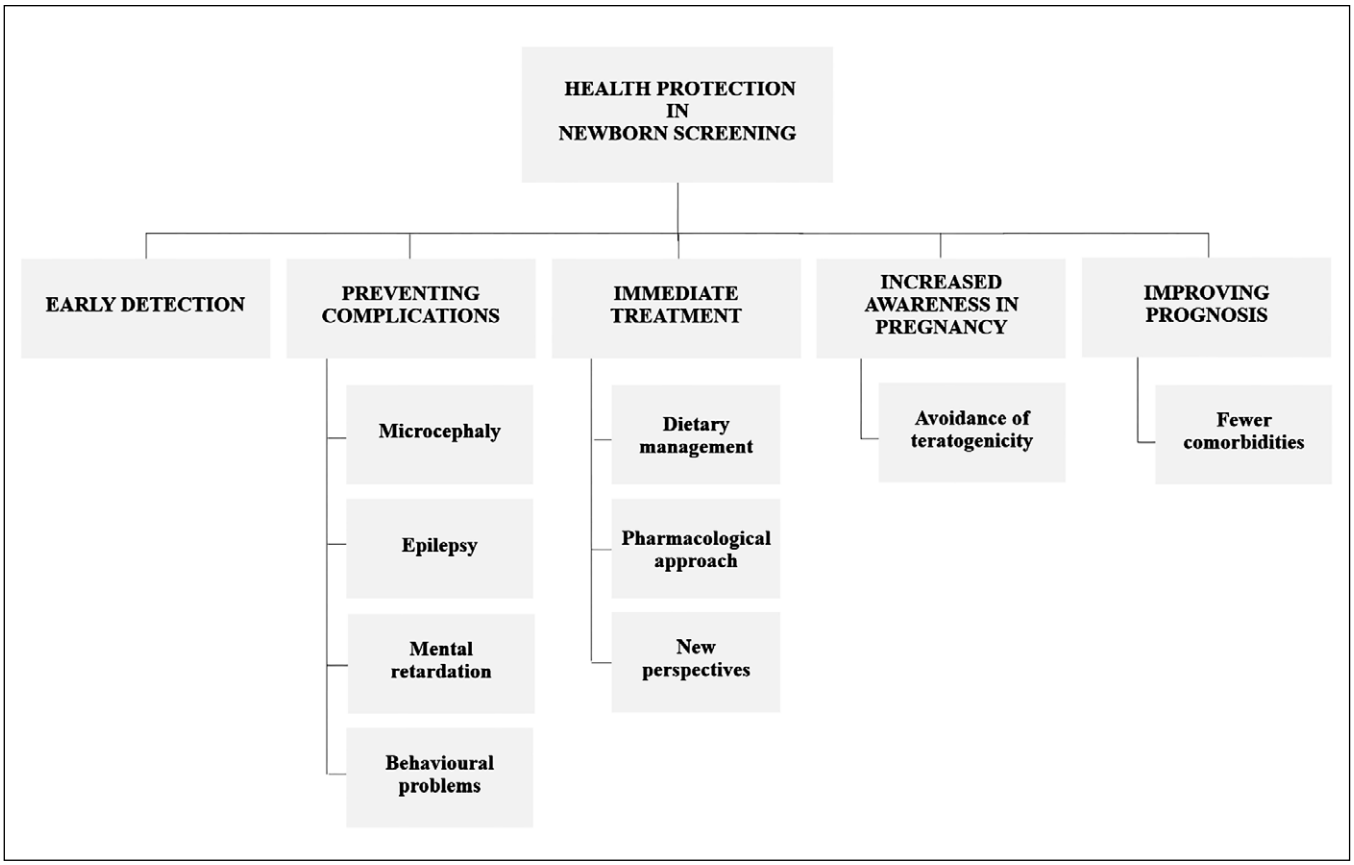

Fig. 1. Phenylketonuria: Key areas of health protection affected by neonatal screening.

lated as follows: "phenylketonuria", "phenylketonuria epidemiology", "phenylketonuria treatment", "newborn screening", "inherited metabolic disorders". All articles retrieved were subjected to analysis.

REVIEW AND DISCUSSION

INHERITED METABOLIC DISORDERS: A MARGINAL OR SIGNIFICANT HEALTH PROBLEM?

Phenylketonuria is one of the most prominent examples of inherited metabolic disorders (IMDs), which comprises over 750 diseases. The majority of these conditions are associated with an abnormality in an enzyme, cofactor or transporter, resulting in impaired functioning of the metabolic pathway [7, 8]. There is a common conception that they are very rare; however, their cumulative incidence is significant [1]. Their number is estimated to be 50.9 per 100,000 live births. Early detection and treatment of metabolic diseases can result in a favourable prognosis. In contrast, undetected and untreated cases have adverse consequences. IMDs are an important cause of mortality in children under the age of five. Approximately 23,500 children die each year from metabolic disease, which represents 0.4% of all child deaths worldwide [9].

MILESTONES IN THE HISTORY OF PHENYLKETONURIA AND NEWBORN SCREENING

The most pivotal event that started the history of metabolic diseases was the discovery of phenylketonuria in 1934 [10]. Dr Fölling examined two siblings who exhibited an intellectual disability and a musty odour. He identified phenylpyruvic acid in their urine. Two decades later, the description of a Phe-reduced dietary regimen marked the beginning of a new era in treatment [11]. Following the creation of a method for the diagnosis

of PKU, newborn screening was first implemented in the United States in 1963 [12]. Subsequently, screening tests were developed for other congenital disorders [13]. Another significant step was the introduction of tandem mass spectrometry (MS/MS) in the 1990s. This analytical technique allows the simultaneous measurement of multiple metabolites in one blood sample. This method has led to the expansion of newborn screening programmes worldwide. Today, approximately 25 million newborns are screened each year using MS/MS [14].

ABOUT NEWBORN SCREENING

The objective of Newborn Bloodspot Screening (NBS) is to identify presymptomatic, treatable congenital conditions at an early stage, allowing for prompt intervention [15]. This is important in preventing potentially severe complications and reducing mortality in infants and children [16]. NBS has evolved from the study of a limited number of disorders to complex programmes that cover over 50 diseases in some countries. In addition to inborn errors of metabolism, these include lysosomal storage disorders, immunodeficiencies, haemoglobin disorders, endocrine disorders, cystic fibrosis, and spinal muscular atrophy [17]. The screening process involves the testing of dried blood spots within the first few days of life [18]. The main motivation for parents to take part in the NBS is the prevention of health problems in their children. One of the primary reasons for declining newborn screening is the concern about potential pain from the heel prick [15]. Failure to inform parents of the purpose of NBS may cause them to opt out without fully understanding the potential risks and benefits [19].

HEALTH PROTECTION – IMPORTANCE OF THE NEWBORN SCREENING

In phenylketonuria, newborn screening plays a crucial role in the context of health protection. Figure 1 illustrates the manner in which NBS impacts health outcomes.

RAPID INTERVENTION FOR BRAIN PROTECTION

Early detection and immediate treatment can prevent the development of serious abnormalities associated with phenylketonuria [6]. Management should be initiated ideally before the age of 10 days [20]. Failure to diagnose and treat PKU can lead to acquired microcephaly, epilepsy and severe cognitive impairment as a result of synaptogenesis defects [4]. Neurological damage becomes irreversible within the first few months or years of life, depending on plasma Phe concentration [6].

THE ESSENCE OF PHENYLALANINE MONITORING IN SUBSEQUENT YEARS

Elevated levels of Phe during late childhood can cause changes in nervous system function, resulting in attention deficit hyperactivity disorder (ADHD), reduced intelligence quotient (IQ), and delayed speech. Adolescents and adults may experience impacts on executive function and mood. Nevertheless, cognitive and behavioural problems can be effectively reversed by maintaining optimal phenylalanine levels [4]. Adherence to treatment may improve intelligence quotient and neuropsychological results [21]. Inadequate management of phenylketonuria may lead to psychological comorbidities, such as phobias and depression [22].

TREATMENT DURATION

The duration of treatment should be determined using objective measurements of blood phenylalanine concentrations. For individuals with Phe blood levels between 360 µmol/L and 600 µmol/L, it is recommended up to the age of 12 years. Lifelong treatment is advised for those with concentrations exceeding 600 µmol/L [23].

DIETARY MANAGEMENT - FUNDAMENTAL OF TREATMENT

The primary treatment for phenylketonuria involves dietary management, specifically limiting natural protein intake and consuming low-protein foods [23]. It is recommended to avoid high-protein products, such as meat, eggs, dairy, cereals, and nuts. The consumption of phenylalanine should be adjusted based on individual tolerance, as determined by test results [24]. Regular monitoring of phenylalanine levels is an essential part of the management of phenylketonuria [25]. Supplementation with medical substitutes, such as Phe-free amino acids (AA) or low-Phe glycomacropeptide (GMP), is used to prevent protein and micronutrient deficiency [26]. The dietary treatment method that shows promise involves supplementing with large neutral amino acids (LNAAs). LNAAs can reduce phenylalanine levels in the brain by competing with phenylalanine for the transporter across the blood-brain barrier [27]. Treatment with these compounds could be an alternative to a demanding low-protein diet in the future [28].

PHARMACOLOGICAL APPROACH AND NEW PERSPECTIVES

Some patients report benefit from pharmacological treatments, such as sapropterin or pegvaliase. Oral

sapropterin is a synthetic form of BH4 that can activate residual PAH and reduce phenylalanine levels when used in conjunction with a controlled diet. However, its effectiveness is limited, with only 20-56% of patients responding to treatment with this medication [29]. Following a lifelong phenylalanine-restricted diet is demanding and burdensome [30]. It is estimated that only 32% of patients follow a Phe-restricted diet with protein replacement as prescribed, the rest are partially compliant or not at all [31]. Furthermore, dining out can pose several difficulties, with the primary obstacle being the restricted availability of low-protein options [32]. A drug that has the potential to improve the long-term outcome and quality of life for patients is pegvaliase. It is an injectable enzyme substitution treatment that degrades phenylalanine. Pegvaliase reduces Phe levels more effectively than standard therapy and allows for greater intact protein intake [29]. However, this treatment requires daily injections and carries the risk of immune-mediated hypersensitivity reactions. Genetic therapies are a promising area of research for directly restoring PAH activity in the liver [33, 34]. Clinical trials are currently underway [33].

INCREASED AWARENESS IN PREGNANCY

It is important for women with phenylketonuria to maintain metabolic control during pregnancy. If phenylalanine levels are high, it can result in maternal phenylketonuria (MPKU) syndrome in the fetus, which is one of the most severe teratogenic pregnancy syndromes [4, 35]. Untreated pregnant women with classical PKU have a 75-90% chance of their offspring developing intellectual disability and microcephaly [4, 36]. Additionally, there is an increased risk of retarded intrauterine growth, congenital heart disease and dysmorphic facial features [35, 37]. Spontaneous miscarriage and early neonatal mortality may also occur [35]. However, controlling the mother's blood phenylalanine levels during pregnancy can prevent MPKU syndrome [36]. It is crucial to monitor phenylalanine levels in the first trimester [37]. The most significant factors for pregnant women to achieve and maintain good metabolic control are the support of loved ones and personalized care from specialist metabolic centres [38].

PROGNOSIS IMPROVEMENT AND ONGOING CHALLENGES

The prognosis for individuals with phenylketonuria has improved significantly thanks to newborn screening and a low-phenylalanine diet [39]. Those who received treatment at a young age are now in their fifth and sixth decades of life and are expected to have a lifespan similar to that of the general population [39, 40]. However, individuals with this condition remain at a heightened risk of developing various health issues, including obesity, hypertension, and osteoporosis [41]. A common comorbidity, particularly in women, is obesity [42]. This condition leads to changes in body composition, including a significant increase in fat content and a decrease in muscle mass, protein, and mineral ingredients [43]. As a result, there may be an increased risk of developing metabolic disorders, such as insulin resistance and dyslipidaemia, which can elevate the likelihood of cardiovascular events [40]. Additionally, individuals with phenylketonuria may have a higher risk of osteoporosis due to low bone mineral density (BMD) [22, 41]. Patients who are diagnosed with PKU at an early age and promptly initiated on appropriate treatment are less prone to developing comorbidities [41].

CONCLUSIONS

The review emphasizes the significance of inherited metabolic disorders, using phenylketonuria as an example, as an important public health concern. Neonatal screening is a crucial aspect of healthcare, with a positive impact on the quality of life and prognosis of patients. Therefore, it is valuable to increase awareness about neonatal screening among parents, so that they can make an informed decision regarding participation. A failure to engage may result in the disease going undetected, which could lead to irreversible neurological complications.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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