Molecular Genetics and Metabolism 99 (2010) S1–S2

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

Introduction

The psychology and neuropathology of phenylketonuria

Numerous advances have been made in our understanding of metabolic disorders over the last century, but optimal outcomes have not been achieved for individuals with phenylketonuria (PKU). We stand now on the cusp of a new era of PKU research and treatment. It is time that we thoroughly reevaluate our understanding of PKU so that we may take advantage of current innovations in neuropsychological assessment (e.g., more sensitive tasks assessing specific executive abilities), scientific technologies (e.g., neuroimaging, genetic sequencing), and treatment options (e.g., large neutral amino acid supplementation, sapropterin dihydrochloride [BH4]) that hold promise for improving quality of life for individuals with PKU.

To achieve this goal, we invited international experts to aid us in assembling a comprehensive overview of the psychology, neuropsychology, and neuropathology of PKU. The reviews and empirical articles presented in this supplement of *Molecular Genetics and Metabolism* represent the work of 50 authors, including psychologists, psychiatrists, geneticists, dietitians, neuroscientists, and biologists from countries all over the world.

Sir Archibald Garrod first described inherited metabolic diseases in 1908 [1], and PKU set the precedent for the identification, understanding, and treatment of such diseases. PKU was first described as "phenylpyruvic oligophrenia" by Følling in 1934, after he identified excess phenylpyruvic acid in the urine of two siblings with mental retardation [2]. Følling's ferric chloride test revealed a characteristic blue–green color in the urine of individuals with PKU. Følling and others, including Penrose who coined the term PKU, used this test to screen patients in psychiatric institutions and to trace the family history of individuals with PKU. This work led to the knowledge that PKU was a rare, recessively inherited disease in which the majority of individuals had intelligence quotients (IQ) less than 50 [2,3–6]. Følling [7] identified elevated blood phenylalanine (Phe) in individuals with PKU, which is the basis for PKU diagnosis today. It was not until the 1940s and 1950s, however, that a clearer picture of the biochemistry of PKU emerged. Major advancement occurred in 1944, when Bernheim and Bernheim [8] demonstrated that the metabolic pathway by which Phe is converted to tyrosine (which we now know is a precursor of dopamine and other neurotransmitters) is disrupted. Another major advancement resulted from the research of Jervis and colleagues [9], who showed that hepatic phenylalanine hydroxylase (PAH) enzyme activity is deficient in individuals with PKU. Three decades later, Woo and colleagues [10] described the first PAH gene sequence, a discovery which was accompanied by optimism that gene therapy might provide a cure for PKU and other metabolic disorders. This excitement was tempered, however, by the realization that genotype–phenotype relationships are complex, and by the significant challenges related to the development of successful gene therapies.

Today, the Phe-restricted diet continues to be the gold standard for PKU treatment, even though this approach is over half a century old. PKU not only set a precedent as the first inherited metabolic defect to be treated, but also the first inherited metabolic defect to be treated through dietary modifications. In 1936, Penrose [11] showed that restricting Phe intake through dietary control of protein consumption decreased Phe metabolites in the urine. However, significant weight loss was associated with decreased protein consumption, and at the time there was no process for creating Phe-free protein supplements to circumvent this problem. In 1943, Schramm and Primosigh [12] used a charcoal filtration method to produce a protein mixture that was free of Phe, tyrosine, and tryptophan. A decade later, Woolf and colleagues [13] suggested supplementing this mixture with tyrosine and tryptophan to create a Phe-free protein mixture that was suitable for treating PKU. Shortly thereafter, Bickel and colleagues [14] first demonstrated that a Phe-restricted diet has a positive impact on the behavior of individuals with PKU and recommended that dietary treatment begin in the neonatal period.

Following the historic report of Bickel and colleagues [14], many efforts focused on optimizing dietary treatment to prevent mental retardation. As such, IQ became a primary endpoint in determining the clinical efficacy of dietary treatment. In reviewing the literature, in 1960 Knox [15] determined that delays in implementing a Phe-restricted diet result in significantly lower IQ. Thus, it was established that dietary treatment should be implemented as early as possible. Unfortunately, at this point in time it remained difficult to diagnose PKU early unless there was a family history of PKU.

In the 1950s, efforts were made in some hospitals to screen all infants for PKU using variations of Følling's ferric chloride test in the urine of wet diapers [16,17]. However, because phenylpyruvic acid is not present in the urine of infants with PKU until after the first few weeks of life, infants were generally discharged from the hospital before screening occurred. This difficulty in screening was compounded by the fact that infants with PKU appear normal at birth, and therefore parents rarely sought medical consultation before noticeable neurological damage occurred.

Guthrie and Susi [18] changed the landscape of PKU diagnosis and treatment in 1963, when they developed a simple laboratory test, the Guthrie bacterial inhibition assay, which detected PKU using dried blood spots from newborns. This test permitted mass screening of infants, early diagnosis of PKU, and implementation of treatment within the first weeks of life. Once again PKU set a precedent, becoming the prototype for subsequent newborn screening programs. PKU screening programs were widely implemented in the late 1960s and early 1970s in most developed countries. MacCready [19] demonstrated that institutions for the

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doi:10.1016/j.ymgme.2009.10.184

mentally retarded included no children born with PKU, since newborn screening had been initiated. Other studies provided equally convincing results documenting prevention of mental retardation, although average IQ was 6–9 points lower in the early-treated children with PKU compared to peers or siblings without PKU [20,21].

The next phase of PKU treatment and research focused on determining the age at which dietary restriction of Phe could be discontinued, and in this regard the assessment of IQ played a major role. Because the Phe-restricted diet was a considerable burden to children and families, and also because brain development was thought to be largely complete by the end of early to middle childhood, many clinics recommended that the diet be discontinued between the ages of 3 and 10 years. In other clinics, dietary restrictions were progressively relaxed as children aged. Few clinics recommended that diet be continued throughout life [22]. After an alarming decline in IQ noted in children with PKU who discontinued treatment in Poland [23], collaborative studies in the United States and Europe compared IQ and academic achievement in diet continued and diet discontinued subjects. These studies documented declines in IQ linked to the elevations in Phe that resulted from the relaxation or absence of a Phe-restricted diet [22,24]. By 1982 over two-thirds of the clinics in the United States recommended that diet be continued for life [25].

Additional impetus for continuing diet for life resulted from research showing that, in spite of IQ in the normal range, children and adults with PKU exhibit deficits in specific neuropsychological abilities. The first indication of such deficits came from studies in which children with early-treated PKU and average IQ were observed to have specific weaknesses in arithmetic and visual-spatial abilities [20,26]. These findings led to increased interest in neuropsychological function [27] and spurred research that demonstrated the negative impact of diet discontinuation on specific neuropsychological abilities [28]. Therefore, in the future, psychological studies will undoubtedly continue to be of great importance in guiding treatment strategies for individuals with PKU.

To our knowledge, this supplement is the first collective review of PKU from a psychological and neuropathological perspective in a journal that focuses on the molecular, genetic, and biochemical bases of disease. Our hope is that this supplement represents the beginning of a new precedent for multidisciplinary, international collaborations that will further elaborate the PKU narrative and improve the lives of individuals with PKU.

For psychologists and others interested in these issues, we invite you to learn more about the newly established Genetics and Metabolism Psychology Network (www.GMPsych.org).

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