Phenylketonuria over the Years: A Story of Treatable Intellectual Disability

Initially described in the 1930s, phenylketonuria (PKU) has become one of the most well-studied inborn errors of metabolism. Widespread newborn screening for PKU began in the mid-1960s and was based on the discovery that a specialized diet can prevent the severe intellectual disability associated with untreated disease. In the 50 years that have elapsed since this pivotal moment in preventative public health, there has been a tremendous transformation in how we understand and treat PKU.

In the 1970s, early newborn screening experience generated a hypothesis of sex-based differences in neonatal phenylalanine metabolism. Wilson et al presented data from California’s first 5 years of newborn screening for PKU that showed that transient hyperphenylalaninemia was independent of sex. To this day, phenylalanine norms are interpreted independent of sex.

Around the same time as the work of Wilson et al was published, there was growing controversy about when to discontinue dietary therapy for PKU. It was becoming apparent that the brain continues to develop into adulthood, and phenylalanine restriction might need to extend past 6 years of age to avoid further cognitive decline.1 Fifty years later, it is now generally accepted that PKU treatment should continue not just through childhood, but for life. Although nutritional management remains the mainstay of therapy for pediatric patients with PKU, novel approaches such as cofactor therapy with sapropterin hydrochloride and enzyme substation therapy with phenylalanine ammonium lyase are transforming PKU’s therapeutic landscape.2

Despite these advances, there is still a great deal of work to be done. Over the coming 50 years, we can aspire to a greater understanding of the age-dependent neuropsychiatric effects of phenylalanine elevations, additional therapeutic alternatives that decrease disease burden, and perhaps a cure with genomic editing.

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