

## Inborn Errors of Metabolism as Mimickers of Pediatric Neuropsychiatric Disorders: Phenylketonuria as an Example

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### Short Communication

Phenylalanine hydroxylase (PAH) deficiency, commonly known as phenylketonuria (PKU), is one of the most common inborn errors of amino acid metabolism. It is inherited as an autosomal recessive trait. Prevalence of PKU is approximately 1:10000 in Europe and 1:15000 in the USA but may vary widely in other regions of the world [1]. Due to the high rate of consanguineous marriages (20-25%) [2], diseases with autosomal recessive inheritance are common in Turkey and estimated incidence of persistent hyperphenylalaninemia is one in 4000-4500 live births [3]. Untreated or late-diagnosed PKU may result in central nervous system damage with varying severity, such as intellectual disability, epilepsy, stereotypical movements, autistic features, learning difficulties and attention-deficit hyperactivity disorder. A diet restricted in phenylalanine and supplemented with medical foods containing phenylalanine-free amino acids can prevent severe neurological sequel if started in the first weeks of life, before signs and symptoms become evident [4]. Since early diagnosis with strict long-term treatment provides the best outcomes, newborn screening programs for PKU have been implemented in many countries around the globe, starting with the state of Massachusetts, USA in 1963 after Robert Guthrie invented the simple bacterial inhibition test using dried blood spots [5]. In Turkey, screening of newborns for PKU has been initiated in 1983 as a pilot study and expanded nationwide in 1993 with 50-60% coverage [3]. Screening by the Ministry of Health with coverage up to 95% and more stringent recording protocols has been in effect since 2006 [6].

We recently described an eight-year-old Turkish boy with normal intelligence who had been diagnosed with dyslexia and attention-deficit hyperactivity disorder, but actually had PKU. He was somehow missed by the newborn screening program in 2006, when coverage rate was around 86% [6]. He had seen a child mental health specialist for hyperactive behaviour, poor school performance and difficulty in reading and writing, and was prescribed methylphenidate with no obvious benefit. He was not investigated for possible organic causes of his complaints and he probably would never have come to our attention had his newborn brother not screened positive for PKU. Family history of this newborn infant prompted us to investigate PKU in his older brother [7].

The phenotypic severity of PAH deficiency mainly depends on the residual activity of the PAH enzyme as determined by the mutations in PAH gene. While mutations completely abolishing enzyme activity may result in classical PKU with severe intellectual deficit, autistic

behaviour and epilepsy, milder mutations may cause asymptomatic mild hyperphenylalaninemia which can only be picked up by screening and does not require treatment [8]. In between, there is a spectrum of varying severity that is proportional to the mean lifetime blood phenylalanine level [9]. Our patient falls somewhere in the middle of this spectrum with relatively mild complaints and many more similar patients may be undiagnosed or misdiagnosed if they were not detected by newborn screening. Therefore, we recommend determination of blood phenylalanine level in all patients with cognitive or behavioural problem of unknown cause, such as autism spectrum disorders, attention-deficit hyperactivity disorder and learning difficulties, especially if there was not an efficient PKU screening program when and where this patient was born [7].

In fact, since we encounter many children born from consanguineous marriages, it is encouraged in our children's hospital to have all children with any behavioural or psychiatric issue evaluated by a pediatrician first before they are referred to a mental health specialist. History, physical examination and some basic biochemical or metabolic investigations may raise suspicion of an underlying organic aetiology. For example, an adolescent with irritability, mood changes, worsening school performance and bad handwriting may turn out to have Wilson disease [10]; another with intellectual disability, autistic behaviour and hyperactivity may be diagnosed with creatine deficiency [11]. Even more importantly, since many inborn errors of metabolism (IEMs) causing intellectual or behavioural problems are potentially treatable, failing to make the correct diagnosis may be extremely harmful to the patient and possibly to future siblings. The reader is referred to a detailed list of treatable IEMs causing intellectual problems [12]. A specific and popular concern is the possibility of underlying IEMs in autism spectrum disorders (ASD). It is known that individuals with PKU, propionic acidemia, Smith-Lemni-Opitz syndrome, mitochondrial disorders may have ASD, usually with additional features [13]. A recent study has proposed that metabolic tests should be included in the work-up of syndromic ASD but not in nonsyndromic ASD [14]. However, we think that screening may be considered for some of the more common and treatable IEMs in patients with ASD or any neuropsychiatric disorder of unknown cause in populations with a high prevalence of IEMs and other Mendelian disorders.

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