

A late-diagnosed phenylketonuria case presenting with autism spectrum disorder in early childhood

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Phenylketonuria is one of the most prevalent autosomal recessive hereditary disorders in Turkey. If untreated, it results in severe brain damage and can also be associated with autism in certain patients. We present a three-year old boy who exhibited the symptoms of autism and was subsequently diagnosed with phenylketonuria. This case illustrates that because the majority of autism cases are idiopathic, an occasional patient with a metabolic disorder might be overlooked especially in the era of newborn screening. We also discuss the possible pathogenetic processes leading to autistic symptoms in phenylketonuria, and wish to draw attention to the possibility of cases missed in the screening program because of less than 100% coverage or insufficient food intake before blood sampling. Clinicians should keep in mind the possibility of treatable disorders in children with autism even when such disorders appear unlikely.

Key words: autism, phenylketonuria, excitotoxicity, glutamate.

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social communication and social interaction associated with restricted repetitive behaviors and interests¹. Its prevalence is about 0.6-2.6%²⁻⁴. Phenylketonuria (PKU) has a prevalence of approximately 1/4,500 in Turkey and is included in the newborn screening program⁵. A group of metabolic disorders including phenylketonuria, histidinemia, adenylosuccinate lyase deficiency, dihydropyrimidine dehydrogenase deficiency, 5'- nucleotidase superactivity and phosphoribosylpyrophosphate synthetase deficiency can be associated with autism⁶. Although the percentage of metabolic disorders in patients with ASD is low, the exact prevalence still remains unknown when we consider the possibly unrecognized metabolic disorders associated with ASD cases⁷. In a study

where Bailei et al.⁸ investigated the presence of autism in a group of patients with early or late diagnosed phenylketonuria, no patients in the early diagnosed group, but two boys (16 and 13 years old respectively) in the late diagnosed group fulfilled the diagnostic criteria. The rate of 6% is rather high in this group of 35 late-diagnosed phenylketonuria patients.

There are pathogenetic processes which mediate the cognitive problems in early diagnosed PKU patients and cause autism and/or mental retardation in the late diagnosed cases. We report a 3-year-old boy with PKU who presented with autism and will discuss the possible pathogenetic processes mediating to autism and other cognitive problems in PKU.

Case Report

This 3 year-old-boy was brought to child

This patient was presented in a poster presentation session at the 2008 National Child and Adolescent Psychiatry Congress in Turkey, titled "Comorbidity of Phenylketonuria and Autism: A case report."

psychiatry clinic with the complaints of speech delay and social problems. He was born to non-consanguineous, healthy parents with induced vaginal delivery at 40 weeks with a birth weight of 3,170 g. He had an uneventful postnatal period, but walked independently around his second birthday. He had no meaningful words, no use of gestures to express himself, and no toilet training yet at the first admission to our clinic. On examination he had poor eye contact, restricted social interaction and stereotyped

hand movements. He had no response when his name was called and was not trying to attract the attention of other people. His neurological examination was unremarkable except hair color lighter than parents. He was diagnosed with autism according to DSM-IV criteria⁹ and etiological investigations were started simultaneously with special education. Sleep EEG was normal. Brain magnetic resonance imaging (MRI) revealed T2 hyperintensity (Fig. 1A) and diffusion restriction consistent with cytotoxic edema in the periventricular white matter, more prominent posteriorly (Fig. 1B, C). Blood and urine amino acid chromatography showed high phenylalanine levels. The diagnosis of PKU was made and diet with restricted phenylalanine was started. At 4 months follow-up improvement was noticed in his eye contact, joined attention and speech. He began to say single words. He was given risperidone 0.25 mg/day for his hyperactivity. In the 7th month of diet he began to understand instructions and duration of joined attention was reported to reach three minutes. He started to point at objects.

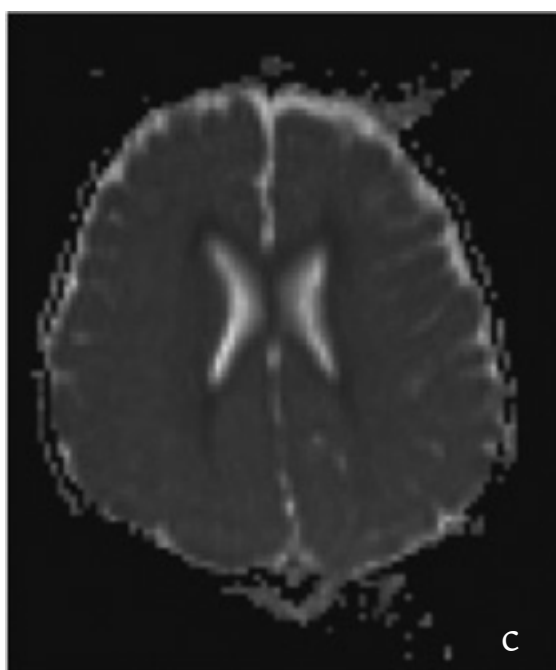
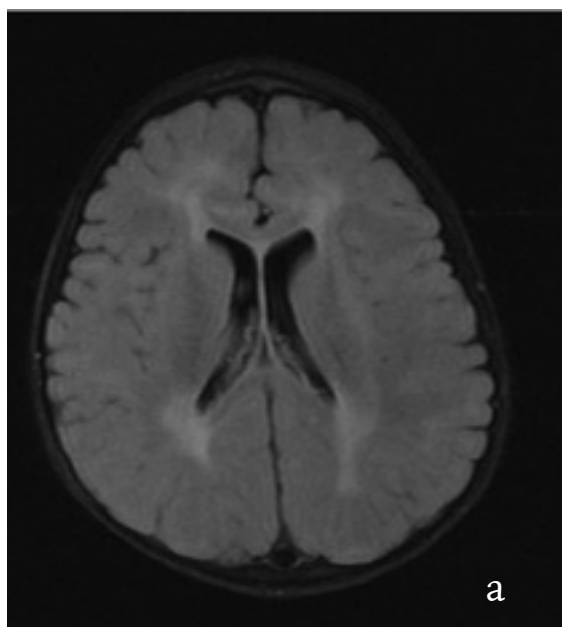


Fig. 1. Brain MRI of the patient. Axial FLAIR (TR/TE/TI; 8000/100/1900 ms) (A) shows hyperintensity in the periventricular white matter, more prominent posteriorly. Diffusion-weighted imaging (DWI) shows hyperintensity of these areas (B) and reduced apparent-diffusion-coefficient (ADC) values (C) suggestive of cytotoxic edema.

His psychometric evaluation (Stanford-Binet) was compatible with mild mental retardation (score: 60-69) when he was 46 months old. He began primary school one year later than his peers and was able to learn reading and writing in the first year. He was given speech therapy for mild speech sound problems. His school success was within normal range, and at the last follow-up at 7 years old, his verbal, performance and total IQ scores with WISC-R were 85, 108 and 96, respectively.

Discussion

This case was not at particular risk for PKU at first thought, being born to non-consanguineous parents and during a period when newborn screening with Guthrie test was widely applied in Turkey. Although the child had a heel prick in the hospital where he was delivered, the results are unavailable and therefore whether his sample was analyzed is questionable. The percentage of babies being screened in Turkey was about 50-60% in those years: it therefore remains unproven whether the sample was analyzed. On the other hand, the possibility of false-negative Guthrie test results at three days of age is low, but not zero¹⁰. False-negative results are mainly due to inadequate feeding of the newborn. It is recommended that the samples should be taken at least after 24-48 hours of feeding after birth to avoid false-negative results. Early sampling is another reason for screening failure.

The possibility of a metabolic disorder including PKU should be considered in any child presenting with symptoms of autism, learning or speech problems and PKU should be tested unless the newborn screening results are available. Even late diagnosed patients benefit from a restricted diet, as in this case who might have had a milder form of PKU and achieved normal school performance.

Yalaz et al.¹¹ reported mental retardation, autistic features, microcephaly, tremor, and motor retardation in a series of 146 patients with phenylketonuria treated at different ages. None of the children treated after 12 months had a normal mental level. On the other hand, some untreated or late-treated patients had mild mental retardation.

Lowe et al.¹² reported two cases with PKU diagnosed with metabolic testing among a

series of 50 autism cases. These two patients' functionality and developmental problems improved after being given a low-phenylalanine diet¹². Although there is no MRI finding specific for PKU, cytotoxic edema of various degree in the white matter is the most prevalent, as in our case. The MRI images of the three autism patients with late diagnosed PKU reported by Bailei et al.⁸ showed hyperintensity of occipital and parietal white matter. Imaging findings are not specific for PKU associated with particular cognitive or neurological symptoms. However the cognitive problems of the patients with frontal and subcortical white matter changes were reported to be more severe compared to the patients whose cerebral white matter lesions were restricted to posterior areas in early-treated phenylketonuria¹³. Contrary to these findings there were PKU patients with cognitive problems although they did not have obvious white matter pathology¹³. Anderson et al.¹³ suggested that these patients might have subtle white matter changes that could not be determined with current MRI technology. White matter changes expected in untreated PKU patients were also reported in an adolescent with early diagnosed PKU who had strict diet control and normal intellectual functioning¹⁴. It is suggested that the cognitive and behavioral phenotype in PKU patients can not only be explained by the presence of white matter lesions. The cognitive profile of PKU is determined by the interaction of environmental, genetic, metabolic, neurological and developmental factors and differs between the cases¹³. White matter abnormalities¹³ and prefrontal dysfunction¹⁵ were also reported in early treated PKU patients.

It is known that there are frontal dysfunction and connectivity problems in cerebral white matter in autism. Considering the connectivity problems and prefrontal dysfunction seen even in early-diagnosed PKU patients, it is not surprising to see autism phenotype in some late-diagnosed PKU patients who might also have additional predisposition genes to autism¹⁵. ADHD, which is highly associated with prefrontal functional problems, is also prevalent in PKU. Christ et al.¹⁵ suggested the prefrontal problems in PKU as a model to study the prefrontal dysfunction in autism and ADHD.

There are several hypothesis for the pathogenetic processes mediating brain damage in PKU. Phenylalanine inhibits Na-K ATPase activity in synaptosomes and lead to chronic intracellular edema of some brain regions through the flow of water from extracellular to intracellular compartment¹⁶. Glutamate excitotoxicity, a common pathway mediating cellular damage in many diseases, is also suggested to be effective in PKU¹⁷. Excessive NMDA receptor binding of glutamate allows calcium influx into postsynaptic neurons and might result in cell death¹⁷. On the other hand the binding of excessive glutamate to non-NMDA receptors leads to influx of sodium into postsynaptic neuron and cytotoxic edema¹⁷. In addition, glial cells carrying these receptors become unable to protect neurons from excitotoxic damage¹⁷. Genetic predisposition facilitating the expression of autism symptoms in some PKU cases cannot be ruled out.

The cognitive problems in PKU were suggested to be related with prefrontal dopamine depletion¹⁸. Phenylalanine competes with tyrosine to cross the blood-brain barrier but the transporters have higher affinity for phenylalanine than for tyrosine which is the aminoacid needed for dopamine synthesis¹⁸. This is the suggested mechanism leading to low dopamine levels at prefrontal in PKU¹⁸. In addition, the negative effect of high phenylalanine levels on glutamate receptor function also contribute to the brain dysfunctioning in PKU^{17,19}. Glushakow et al.¹⁹ showed that high levels of phenylalanine selectively and significantly depress the function of glutamate receptors in excitatory synapses. They suggested three different mechanisms mediating this effect of phenylalanine: 1) Attenuation of glutamate release from the presynaptic neuron, 2) competition for glycine binding site of NMDA receptors, 3) competition for the glutamate binding site of non-NMDA receptors. In summary, when we consider the important effects of glutamate receptors in activity dependent synaptic plasticity, long-term memory and associative learning, the impairment of glutamate receptor activity seems to be highly contributing to the brain dysfunction in PKU¹⁹.

Phenylketonuria patients might partially leave phenylalanine restricted diet at adolescence. Anderson et al.¹³ reported a relationship

between life-time phenylalanine levels and impaired cognitive functions seen in a group of patients with extensive white matter abnormalities. Considering the effects of high phenylalanine concentration on brain, it seems that this harmful effect of phenylalanine on cognitive functions can only be prevented with strict adherence to diet during life-time.

Clinicians should think of metabolic testing with urine-blood aminoacid chromatography, or tandem mass spectrometry in cases with autism or learning difficulties even in the absence of intellectual disability and even in the era of newborn metabolic screening in order not to overlook treatable conditions.

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