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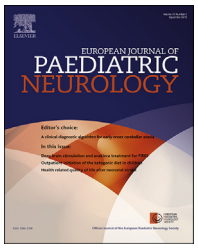

Editorial

Sleep disorders in phenylketonuria

Phenylketonuria (PKU) is an autosomal recessive metabolic disorder caused by deficient activity of the enzyme L-phenylalanine-4-hydroxylase, which catalyses the irreversible conversion of phenylalanine (Phe) to tyrosine. PKU is usually detected by newborn screening, enabling early diagnosis and treatment which prevent the intellectual disability and other typical manifestations of the disease. However, there are factors affecting the quality of life of patients that are poorly understood. Even following Phe-restrictive dietary recommendations for all age groups, evidence suggests that PKU management has resulted in sub-optimal outcomes, including slight deficits in neurocognitive and psychosocial metrics. As a result of the enzymatic deficiency, the metabolic pathway of phenylalanine is disrupted, and the high blood and brain concentrations of phenylalanine impair the transport of large neutral amino acids across the blood–brain barrier (i.e., tryptophan-serotonin precursor- and tyrosine -dopamine precursor-). This impaired availability of biosynthesis precursors induces dopamine and serotonin deficiencies. Because of the key role as sleep modulators of both neurotransmitters, it is reasonable to think that PKU patients are therefore a population at risk for sleep disorders.

It is well established that adequate sleep is essential for general healthy functioning and altered sleep negatively influences neurobehavioral functioning, including lapses of attention, slowed working memory, reduced cognitive throughput, depressed mood, and perseveration of thought.

It has been demonstrated that PKU adult patients have a higher prevalence of sleep problems, a reduced sleep quality, and an increased latency to fall asleep and experience more sleepiness during the day.[1] Prevalence of sleep disturbance in PKU adults patients aged 20 to >80 years is 14.4% vs 6.9% in general population.[2] However, this increased prevalence of sleep problems is not observed in early-treated PKU children and adolescent patients. The prevalence of sleep disorders in this age group is similar to that found in the general population (12.5%, mean age 12 years), despite the fact they present with dopamine and serotonin deficits.[3] Several possible explanations of this apparent age-dependent prevalence of sleep problems in PKU patients can be kept in mind. More exposure over time or a greater deficit of neurotransmitter synthesis could be necessary to induce a sleep disorder, and therefore, sleep disorders would be more frequent in adults than in young early treated PKU patients. However, another reasonable explanation could be that these abnormalities in neurotransmitter availability are not specifically linked to possible sleep problems; in treated and untreated PKU patients, sleep-EEG measurements indicate differences in the number of sleep spindles despite similar REM and non-REM distribution compared to healthy controls.[4] Finally, in studies using the PKU mouse model, high levels of orexin A (hypocretin 1) were reported. This neuropeptide has a key role regulating the sleep–wake cycle and has been associated with wakefulness.[5] Further longitudinal studies to deepen in the pathophysiology of these disorders are needed.

A better understanding of the presence and severity of sleep disturbances in PKU patients, with the habitual clinical use of sleep disturbance scales, and its pathophysiology could lead to the improvement of treatment strategies by including sleep quality as an additional treatment target.

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