ADHD symptoms in neurometabolic diseases: Underlying mechanisms and clinical implications

Selina Cannon Homaei [1], Helene Barone [2], Rune Kleppe [3], Nibal Betari [4], Andreas Reif [5], Jan Haavik [6]

AFFILIATIONS

[1]Division of Psychiatry, Haukeland University Hospital, Norway; Department of Biomedicine, University of Bergen, Norway. Electronic address: selina.homaei@uib.no.
[2]Regional Resource Center for Autism, ADHD, Tourette Syndrome and Narcolepsy, Western Norway, Division of Psychiatry, Haukeland University Hospital, Norway. Electronic address: helenehalleland@gmail.com.
[3]Division of Psychiatry, Haukeland University Hospital, Norway; Norwegian Centre for Maritime and Diving Medicine, Department of Occupational Medicine, Haukeland University Hospital, Norway. Electronic address: rune.kleppe@helse-bergen.no.
[4]Department of Biomedicine, University of Bergen, Norway. Electronic address: nibal.betari@uib.no.
[5]Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, University Hospital Frankfurt, Frankfurt am Main, Germany. Electronic address: andreas.reif@kgu.de.
[6]Division of Psychiatry, Haukeland University Hospital, Norway; Department of Biomedicine, University of Bergen, Norway. Electronic address: jan.haavik@uib.no.

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Abstract

Neurometabolic diseases (NMDs) are typically caused by genetic abnormalities affecting enzyme functions, which in turn interfere with normal development and activity of the nervous system. Although the individual disorders are rare, NMDs are collectively relatively common and often lead to lifelong difficulties and high societal costs. Neuropsychiatric manifestations, including ADHD symptoms, are prominent in many NMDs, also when the primary biochemical defect originates in cells and tissues outside the nervous system. ADHD symptoms have been described in phenylketonuria, tyrosinemias, alkaptonuria, succinic semialdehyde dehydrogenase deficiency, X-linked ichthyosis, maple syrup urine disease, and several mitochondrial disorders, but are probably present in many other NMDs and may pose diagnostic and therapeutic challenges. Here we review current literature linking NMDs with ADHD symptoms. We cite emerging evidence that many NMDs converge on common neurochemical mechanisms that interfere with monoamine neurotransmitter synthesis, transport, metabolism, or receptor functions, mechanisms that are also considered central in ADHD pathophysiology and treatment. Finally, we discuss the therapeutic implications of these findings and propose a path forward to increase our understanding of these relationships.

Keywords: Amino acids; Attention Deficit Hyperactivity Disorder (ADHD); Brain; Dopamine; Energy; Metabolic diseases; Mitochondrial dysfunction; Norepinephrine; Phenylketonuria (PKU); Tyrosinemia.