Inborn Errors of Metabolism with Movement Disorders

Defects in Metal Transport and Neurotransmitter Metabolism

Trishna Kantamneni, MD, Lileth Mondok, MD, Sumit Parikh, MD*

KEYWORDS

• Metal transport • Neurotransmitter metabolism • Pediatric movement disorders

KEY POINTS

- Movement disorders in pediatric age group are largely of the hyperkinetic type.
- Metal ion accumulation in the central nervous system presents predominantly with movement disorders and over time leads to psychomotor decline.
- Abnormalities in monoamine and amino acidergic neurotransmitter metabolism present in individuals with a combination of abnormal movements, epilepsy, and cognitive and motor delay.
- Detailed clinical history, careful examination, appropriate diagnostic work-up with metabolic screening, CSF neurotransmitters, and targeted genetic testing help with accurate diagnosis and appropriate treatment.

INTRODUCTION

Movement disorders in the pediatric age group are a diverse group of conditions that lead to abnormal involuntary movements usually associated with abnormalities or injury to the basal ganglia and its connections and are seen in a variety of neurologic disorders. Movement disorders in children are usually divided into two main groups: hyperkinetic/dyskinetic (chorea, athetosis, tremor, ballismus, myoclonus, tics, and stereotypies)[1] movement disorders (**Table 1**); and hypokinetic movement disorders, which include the parkinsonian phenotypes. Hypokinetic disorders are uncommon in the pediatric population but are seen with select genetic conditions, such as mitochondrial disease. Abnormal movements can be the main presenting feature of a disease or can occur as a late manifestation.

A broad approach to evaluating movement disorders in children is dividing them into acquired and hereditary causes. Abnormal involuntary movements secondary to

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Department of Neurology, Neurological Institute, Center for Pediatric Neurology, Cleveland Clinic, 9500 Euclid Avenue, S60, Cleveland, OH 44195, USA
* Corresponding author.
E-mail address: parikhs@ccf.org

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Table 1
Hyperkinetic movements

Dystonia	Involuntary sustained or intermittent muscle contractions cause twisting and repetitive movements, abnormal postures, or both.
Chorea	Ongoing random-appearing sequence of one or more discrete involuntary movements or movement fragments.
Athetosis	Slow, continuous, involuntary writhing movement that prevents maintenance of a stable posture.
Myoclonus	Sequence of repeated, often nonrhythmic, brief shock-like jerks caused by sudden involuntary contraction or relaxation of one or more muscles.
Tremor	Rhythmic back-and-forth or oscillating involuntary movement about a joint axis.

From Sanger TD, Chen D, Fehlings DL, et al. Definition and classification of hyperkinetic movements in childhood. Mov Disord 2010;25(11):1538–49; with permission.

medications, infectious or postinfectious etiology, or other structural neurologic lesions (stroke, neonatal hypoxic ischemic encephalopathy, kernicterus) are more common causes and should be evaluated thoroughly especially in acute or subacute presentations. A progressive disease course with prominent developmental delays, cognitive decline, and psychiatric features combined with an abnormal neurologic examination is highly suspicious for an underlying metabolic disorder as the primary cause of a movement disorder. Almost all categories of inborn errors of metabolism can potentially have a type of movement disorder as a symptom. **Box 1** lists some of the common inborn errors of metabolism that present predominantly with abnormal movements. This article in particular provides an overview of inborn errors of metal transport and neurotransmitter metabolism that have movement disorder as the primary manifestation of disease.

A meticulous history and physical examination, especially proper identification of the presenting movement disorder, are the essential tools in arriving at the correct diagnosis. Ancillary testing with neuroimaging, cerebrospinal fluid (CSF) studies, and genetic testing is largely dependent on the degree of clinical suspicion and should be used as such to provide the highest diagnostic yield.

DISORDERS OF METAL TRANSPORT

Movement disorders in the pediatric population secondary to metallic ions are primarily caused by excessive accumulation and deposition of the substance in the brain leading to a disruption of normal anatomy and physiology. Deficiency states of these metals can also cause neurologic symptoms but typically not primarily movement disorders. The most common conditions involve an abnormal increase in iron, copper, and manganese.

Iron

Iron deposition in the basal ganglia, specifically the globus pallidus and substantia nigra, can cause either a hypokinetic or hyperkinetic movement disorder. These disorders have been termed neurodegeneration with brain iron accumulation (NBIA) and share the key feature of iron accumulation in the brain on pathology with associated dystonia, spasticity, parkinsonism, and psychiatric symptoms. NBIA disorders include several different conditions with pantothenate kinase–associated neurodegeneration (PKAN; previously known as Hallervorden-Spatz disease) being the most common.

PKAN was initially described by Hallervorden and Spatz in 1922. The disorder was later renamed to PKAN as Dr. Hallervorden and Spatz had actively collected and