Inborn Errors of Metabolism with Seizures

Defects of Glycine and Serine Metabolism and Cofactor-Related Disorders

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KEYWORDS

• Inborn errors of metabolism • Seizures • Epilepsy • Myoclonic epilepsy • Glycine • Serine • Pyridoxine

KEY POINTS

- Inborn errors of metabolism (IEM) are relatively uncommon causes for seizures in children; however, they should be considered in the differential diagnosis because several IEM are potentially treatable and seizures can be resolved when appropriate treatment is initiated.
- IEM should be particularly considered in neonatal seizures and in the context of refractory seizures. Other clues from clinical presentation, physical examination, laboratory tests, and brain imaging can increase the possibility of IEM.
- Several IEM can present with seizures, either as the main presenting finding or as a part of a more complex phenotype.
- IEM that cause seizures include cofactor-related disorders (eg, pyridoxine-dependent epilepsy, pyridoxal phosphate-responsive epilepsy, and cerebral folate deficiency), glycine and serine metabolism defects (eg, glycine encephalopathy and serine biosynthesis defects), and other disorders (eg, glucose transporter type 1 deficiency, adenylosuccinate lyase deficiency, and guanidinoacetate methyltransferase deficiency).
- When IEM are suspected, diagnosis and treatment should be simultaneous. Early treatment can prevent, or at least minimize, long-term sequelae.

INTRODUCTION

Seizures are frequently encountered in pediatric practice with an estimated prevalence of 1% in children.[1] The etiologic factors of seizures are many, including genetic diseases; structural brain abnormalities; or acquired conditions such as infections, tumors, and trauma. Alternatively, seizures can be secondary to provoking factors such

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as fever and hypoglycemia.[2] Inborn errors of metabolism (IEM) are relatively uncommon causes for seizures in children (**Box 1**). They still should be always considered in the differential diagnosis because several IEM that cause seizures are potentially treatable (**Box 2**) and seizures can be resolved when appropriate treatment is initiated. IEM often require specialized dietary and therapeutic interventions that should be initiated in a timely manner to prevent, or at least minimize, long-term sequelae. Even with

Box 1
Inborn errors of metabolism that can present with seizures

- Cofactor-related disorders
  - Pyridoxine-dependent epilepsy
  - Pyridoxal phosphate-responsive epilepsy
  - Cerebral folate deficiency
  - Biotinidase deficiency
  - Holocarboxylase synthetase deficiency
  - Molybdenum cofactor deficiency
  - Severe methylenetetrahydrofolate reductase (MTHFR) deficiency
- Amino acid disorders
  - Glycine encephalopathy
  - Serine biosynthesis defects
  - Sulfite oxidase deficiency
  - Urea cycle disorders
  - Phenylketonuria
  - Organic acidemias
  - Maple syrup urine disease
- Metal transport
  - Menkes disease
- Lysosomal disorders
  - Neuronal ceroid lipofuscinosis
  - Sialidosis type I and type II
  - Metachromatic leukodystrophy
  - GM1 gangliosidosis
  - GM2 gangliosidosis
  - Gaucher disease types 2 and 3
  - Niemann-Pick disease type C
- Disorders of energy metabolism
  - Mitochondrial disorders
  - Guanidinoacetate N-methyltransferase (GAMT) deficiency
  - Disorders of pyruvate metabolism
  - Glucose transporter type 1 (GLUT-1) deficiency
  - Fatty acid oxidation disorders[a]
  - Disorders of gluconeogenesis[a]
  - Glycogen storage disorders[a]
- Disorders of purine and pyrimidine nucleotides metabolism
  - Adenylosuccinate lyase (ADSL) deficiency
  - Lesch-Nyhan syndrome
  - Dihydropyrimidine dehydrogenase deficiency
- Peroxisomal disorders
  - Zellweger syndrome
  - X-linked adrenoleukodystrophy
- Congenital disorders of glycosylation

[a] In these disorders, seizures are secondary to hypoglycemia.