

# HOSPITAL PHYSICIAN®

## NEUROLOGY BOARD REVIEW MANUAL

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The *Hospital Physician Neurology Board Review Manual* is a study guide for residents and practicing physicians preparing for board examinations in neurology. Each quarterly manual reviews a topic essential to the current practice of neurology.

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## Metabolic Disorders in Pediatric Neurology

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# Metabolic Disorders in Pediatric Neurology

Gregory M. Rice, MD, and David Hsu, MD, PhD

## INTRODUCTION

This manual reviews metabolic diseases that affect the nervous system, focusing on the usual presentations from the perspective of a pediatric neurologist. Many of these disorders also have milder presentations in later life, which are not discussed here. This review presents sufficient information to begin a workup and to institute initial interventions. A beginning neurologist will need to learn more about each disorder as he or she closes in on the definitive diagnosis. If a diagnosis is not readily apparent by clinical presentation (**Table 1**), one must resort to a more systematic approach.

In this review, disorders are generally grouped according to defects of the various biochemical pathways (**Figure 1**). Metabolic disorders caused by energy failure can involve defects in the mobilization of glycogen (ie, *glycogen storage diseases*) or fats (ie, *fatty acid oxidation defects*) or defects in the citric acid cycle or respiratory chain (ie, *mitochondrial disorders*). These disorders tend to present as decompensations with stress or increased energy demand. Metabolic disorders caused by defects in amino acid metabolism include the *organic acidemias*, *aminoacidopathies*, and *urea cycle defects*. These disorders tend to present in infancy as increasing lethargy and vomiting with initiation of feeds. *Lysosomal disorders* result in the accumulation of large carbohydrate-lipid complexes and present as dysmorphism with organomegaly, psychiatric symptoms, or white matter disease. Aside from the glycogen storage disorders, the *disorders of carbohydrate metabolism* are rather heterogeneous. Finally, some primarily *white matter disorders* are suggested by clinical presentation, such as increasing spasticity and abnormalities in white matter on magnetic resonance imaging (MRI), whereas primarily *gray matter disorders* present as seizures and cognitive decline.

In the United States, most states screen newborns for phenylketonuria, galactosemia, hypothyroidism, congenital adrenal hyperplasia, hemoglobinopathies, and maple syrup urine disease. Some states employ tandem mass spectroscopy, which gives amino acid and acylcarnitine profiles. These tests are useful for diagnosing many metabolic disorders, as described below.

## DISORDERS CAUSED BY ENERGY FAILURE

### GLYCOGEN STORAGE DISORDERS (GSD)

Glycogen is an important source of stored glucose found primarily in liver and muscle. Defects in glycogen mobilization can lead to energy failure during times of fasting and exercise.

#### GSD Type II

GSD type II (Pompe's disease) is caused by deficiency of the lysosomal enzyme acid maltase ( $\alpha$ -1-4-glucosidase).<sup>1</sup> The infantile form presents as severe hypotonia and cardiomyopathy and is usually fatal before 12 months of age. The childhood form affects only skeletal muscle and presents as progressive weakness. Creatine kinase (CK) levels are markedly elevated, and muscle biopsy demonstrates glycogen storage in muscle fibers and absence of acid maltase. Hypoglycemia is not seen in GSD type II.

#### GSD Type V

GSD type V (McArdle's disease) is caused by deficiency of myophosphorylase and presents in adolescents as cramps and muscle fatigue shortly after initiating exercise. A "second wind" effect can occur (ie, renewed ability to continue exercising if patients rest briefly after the onset of fatigue). Laboratory studies show elevated CK levels, post-exertional myoglobinuria, and a failure of the normal rise in lactate levels with exercise. The forearm ischemic test is the classic exercise test but is difficult to perform reliably. Muscle biopsy shows glycogen storage in muscle and absence of myophosphorylase. Moderate exercise with careful warmup is advisable. Dietary treatments have been disappointing.

### FATTY ACID OXIDATION DISORDERS

Fatty acid oxidation disorders consist of autosomal recessive defects in either the transport of fatty acids into mitochondria or in the intramitochondrial  $\beta$ -oxidation of fatty acids. A prolonged fast or significant stress (eg, illness, surgery) may deplete liver stores of glycogen. If fatty stores fail to be mobilized for fuel, the result is the classic laboratory finding of *hypoketotic hypoglycemia*.<sup>2</sup> A mild to