Clinical Neurogenetics

Neurologic Presentations of Metabolic Disorders

Jennifer M. Kwon, MD[a,b,*], Kristin E. D'Aco, MD[c]

KEYWORDS

• Metabolic genetics • Amino acid disorders • Organic acid disorders
• Urea cycle defect • Small molecule disorder • Inborn error of metabolism

KEY POINTS

- Inherited metabolic disorders are rare causes of neurologic disease, but they should always be considered because many are treatable.
- The characteristics of treatable metabolic disorders are:
  - Although their clinical presentations are often seen early in line with abrupt onset, these can present subacutely during later childhood and adult years
  - Episodic relapses
  - Nonspecific clinical/physical features
- Although many are identified through newborn screening programs, specific screening for inherited metabolic disorders remains useful.

Case

The patient was a previously healthy, successful attorney who developed social withdrawal and difficulty with calculations at age 45 years.[1] Over the subsequent months, he had problems with social interactions and became lost easily. Six months after presentation, he was alert but could not recall items after 5 minutes and had trouble initiating speech. His motor function, sensation, and coordination were normal.

His family history was notable for a brother who had developed progressive leg weakness and numbness with incontinence in his 30s. He had no dementia; he died of complications of frequent urinary tract infections.

The patient and his brother may have had dissimilar presentations but their brain magnetic resonance imaging (MRI) was notable for periventricular, nonenhancing, increased signal

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[a] Division of Child Neurology, Department of Neurology, University of Rochester Medical Center, Rochester, NY, USA; [b] Division of Child Neurology, Department of Pediatrics, University of Rochester Medical Center, Rochester, NY, USA; [c] Division of Medical Genetics, Department of Pediatrics, Golisano Children's Hospital, University of Rochester Medical Center, Rochester, NY, USA
* Corresponding author. Division of Child Neurology, Department of Neurology, University of Rochester Medical Center, 601 Elmwood Avenue, Box 631 (Child Neurology), Rochester, NY 14642.
E-mail address: jennifer_kwon@urmc.rochester.edu

Neurol Clin 31 (2013) 1031–1050
http://dx.doi.org/10.1016/j.ncl.2013.04.005 **neurologic.theclinics.com**
0733-8619/13/$ – see front matter © 2013 Elsevier Inc. All rights reserved.

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abnormalities on T2-weighted imaging confluent in the occipital lobes (despite the brother's myelopathic presentation, his spine MRI was normal).

The patient's initial evaluation included cerebrospinal fluid (CSF) showing increased protein (61 mg/dL, normal 15–45 mg/dL), normal CSF immunoglobulin G index, and no oligoclonal bands. Thyroid and cortisol function were normal. Electroencephalogram (EEG) was normal. Hemoglobin; mean corpuscular volume; erythrocyte sedimentation rate; and vitamins E, B_{12}, and folate levels were normal.

Although the patient could have had an acquired condition, the family history suggested an inherited disorder of myelin. In this situation, neurologists should consider disorders arising from defects in metabolism at the organelle level, such as metachromatic leukodystrophy and peroxisomal disorders, or at the small molecule level, such as organic acidemias and urea cycle defects. Although the latter category of disorders are rare in neurologic practice, they are important because they are often treatable.

Additional testing showed plasma homocysteine, 220 μM (normal <20 μM) and methylmalonic acid, 1051 μM (normal <30 μM). These results helped to diagnose this patient with a form of combined methylmalonic aciduria (MMA) and homocystinuria caused by a cobalamin (Cbl) C defect. The patient showed improvement with cobalamin injections, a treatment that might have saved his brother's life.

SMALL MOLECULE DISORDERS: OVERVIEW

The small molecule disorders described later are caused by enzyme defects in pathways of intermediary metabolism (in contrast with the organelle disorders exemplified by lysosomal storage diseases).[2,3] These disorders tend to present early in life, often with abrupt onset with encephalopathy and metabolic crises. Apart from the history of obtundation, vomiting, acidosis, or hyperammonemia, there are few other physical or neurologic findings that are specific for these disorders.

Although they are rare causes of neurologic disease, they remain important because, with prompt identification, there can be effective treatment. For this reason, current newborn screening programs identify many of these conditions.

Disorders of small molecules that are particularly likely to be seen by neurologists include those associated with defects in amino acid metabolism: organic acidemias, aminoacidopathies, and urea cycle defects (**Fig. 1**). The diseases described in this article represent a subset of the biochemical genetic abnormalities likely to be encountered by neurologists. Certain treatable disorders, such as defects of fatty acid oxidation, are not included, despite their frequency in the population. Other disorders of small molecule metabolism will be are discussed as additional examples in which early treatments have the potential for better outcomes.

DEFECTS OF AMINO ACID METABOLISM

Introduction: Clinical Aspects

Disorders of amino acid metabolism tend to be sudden in onset, characterized by episodic relapses and remissions, with nonspecific physical findings. They may respond rapidly to appropriate treatment. If left untreated, many of these disorders develop a more chronic progressive neurologic picture reminiscent of disorders of organelle metabolism. Metabolic screening (**Tables 1** and **2**) in blood and urine may detect many small molecule disorders. In nearly all these cases, the short-term and

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