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Review article

Adolescent Presentations of Inborn Errors of Metabolism

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A B S T R A C T

Several studies have shown that a large percentage of inborn errors of metabolism is present in adolescent patients. Individually, each diagnosis in this category of diseases is rare; therefore, there is often a significant delay in determining the etiology of a patient's complaints. These disorders can have a wide variety of multisystemic presentations, several of which overlap with more common disorders of adolescence. This review highlights the red-flag findings on history and physical examination indicating a possible inborn error of metabolism. In addition, a systematic approach for evaluating and categorizing these disorders is introduced and demonstrated through case examples. Primary care physicians play a crucial role in the early detection and prompt treatment of patients with late-onset inborn errors of metabolism.

IMPLICATIONS AND CONTRIBUTION

Inborn errors of metabolism presenting in adolescence often are missed because of their low prevalence and high clinical variability. Identifying red-flag signs and symptoms of inborn errors is an essential skill for clinicians who care for adolescent and young adult patients with complex, atypical, or puzzling undiagnosed conditions.

Inborn errors of metabolism (IEM) are caused by enzyme or cofactor abnormalities that result in accumulations of toxic intermediate products or deficiencies of essential end products. Historically, IEM were considered rare diseases occurring in less than 1 per 100,000 live births and presenting during infancy or early childhood. Epidemiologic studies in the past 15 years indicate both higher incidence rates and older ages at presentation than previously suspected. A 2003 study in United Kingdom revealed that IEM occurred in up to 20 per 100,000 live births and that 37% of IEM diagnoses were made in patients older than 10 years [1]. The estimated cumulative incidence of IEM ranges from 1 per 750 to 2,500 live births, and the true incidence is thought to be much higher because of underrecognition of clinical manifestations and limitations in diagnostic testing.

Several factors complicate IEM diagnosis during adolescence. First, clinical manifestations tend to decrease in acuity and severity with advancing age at diagnosis. Second, there is considerable overlap in the manifestations of uncommon IEM and common nonmetabolic disorders of adolescents. Third, IEM can involve almost any organ system or developmental process and can present as chronic, acute, or waxing-and-waning symptoms triggered or exacerbated by seemingly minor stresses or events [1–4].

In this article, we review aspects of the adolescent history and physical examination that should alert the clinician to the possibility of an IEM. Next, we suggest a strategy to help organize and understand the pathogenesis of these disorders. In the final section, we present three cases to illustrate the application of this strategy to the evaluation of adolescents with possible IEM.

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Review of the Literature

Red flags for inborn errors of metabolism

Table 1 lists six red flags that should prompt consideration of an IEM in an adolescent patient: unexplained episodic symptoms; decompensation when stressed; failure to thrive in conjunction with other symptoms; symptoms referable to high-energy organs (i.e., brain, heart, muscle, and liver); avoidance of certain foods; and family history of unexplained childhood deaths or symptoms similar to those of the adolescent.

Past medical history of unexplained episodic symptoms that worsen or are precipitated by physiologic stress should prompt consideration of an IEM. Potential stresses include puberty, acute illness, fasting, dietary change, dehydration, exercise, surgery, trauma, and pregnancy [5,6]. These stressors can induce catabolism or tissue breakdown releasing sugar, fat, and proteins into the bloodstream. Several IEM involve the defective processing of these nutrients and subsequent accumulation of toxic metabolites. Review of systems may reveal current or past complaints of symptoms referable to organs with high-energy utilization (i.e., brain, muscle, heart, and liver). Growth charts may demonstrate delays or plateaus in height and/or weight curves.

A thorough dietary history can also suggest the presence of an IEM. By adolescence, individuals with IEM may have learned to avoid foods they cannot metabolize. Individuals with undiagnosed late-onset urea cycle defects may avoid meats and other proteins to minimize the accumulation of unprocessed nitrogen. Those with undiagnosed hereditary fructose intolerance may avoid fruits, fruit juices, table sugar, and other fructose-containing foods.

A three-generation family history can help narrow the differential diagnosis of a suspected IEM. Because most IEM are autosomal recessive, affected families may be unrecognized for generations. Consanguinity increases the likelihood of disease expression. Disease expression in multiple maternal male relatives suggests X-linked inheritance. Disease expression in multiple maternal male and female relatives suggests a mutation in mitochondrial DNA, which is maternally inherited. Mutations in nuclear-encoded genes can also cause mitochondrial disease. However, unlike mitochondrial DNA mutations, nuclear mutations follow an autosomal recessive (or rarely autosomal dominant) pattern of inheritance.

Newborn screening and adolescents

A negative newborn metabolic screen does not exclude the presence of all IEM. Decisions about which conditions to include in newborn screening and the management of abnormal test results vary across public health districts. The first newborn metabolic screen was implemented in the 1960s to detect phenylketonuria and prevent the associated developmental delay through the early implementation of a low-phenylalanine diet [7,8]. Newborn screening in the United States has expanded to include at least 20 disorders in which early detection and therapy is beneficial [9–11].

Table 1
Red flags for metabolic disease

Unexplained episodic symptoms
Decompensation during stress or illness
Failure to thrive
Symptoms in high energy utilizing organs such as brain, heart, liver, muscle
Avoidance of certain foods
Family history of symptoms or early childhood death

An example of a treatable disease on the newborn screen is biotinidase deficiency. This disorder results in an inability to reuse biotin and causes neurologic deterioration if left untreated. Supplementation with biotin prevents this deterioration but requires early initiation and lifelong adherence. An adolescent with biotinidase deficiency whose parents have monitored the biotin supplementation since birth may experience symptoms for the first time if adherence wanes with increasing autonomy.

Newborn screening also includes several disorders whose natural histories vary widely across individuals. Some disorders of fat metabolism can present in infancy with life-threatening metabolic decompensation or in adolescence with mild rhabdomyolysis. An adolescent with a metabolic condition detected on newborn screening may be asymptomatic but remains at risk for late-onset disease.

Although newborn screening is designed to be a high-sensitivity test, there are published cases of false negative results [12,13]. A recent study of expanded newborn screening in New South Wales, Australia revealed that 15 of 1,500,000 babies screened for selected metabolic disorders had negative newborn test results and subsequent diagnoses of target conditions [14].

In summary, newborn screening is not designed to detect all IEM. Rare false negative results are possible. Consequently, a normal newborn screen does not definitively rule out an IEM. However, an adolescent health care provider meeting a new patient should ask if the newborn screen was normal and obtain a record of the result.

Classifying inborn errors of metabolism

IEM can be a daunting topic for clinicians because of the number of disorders and the biochemical complexity of each disorder. Excellent classification schemes have been developed to help categorize and understand IEM [15]. The following two basic questions can help clinicians use these classification systems: where is the defect and how does the defect lead to disease? Most IEM are due to a metabolic defect in one of three general catabolic pathways responsible for the breakdown of protein, sugar, and fat. Symptoms result from the accumulation of toxic metabolites and/or the production of insufficient energy. Figure 1 depicts the simplified major catabolic pathways within a cell. IEM involving large, complex macromolecules (e.g., lysosomal storage diseases, peroxisomal biogenesis disorders) also occur but are beyond the scope of this review.

Consider two adolescent patients with different, undiagnosed IEM who present with similar, new-onset symptoms of confusion and unsteady gait. In the first patient, symptoms developed after the initiation of a high-protein diet. This history suggests a urea cycle defect that disrupts the catabolism of protein. The urea cycle converts ammonia from protein to urea for excretion by the kidney. Hyperammonemia and illness developed in the first patient when the ingested protein load exceeded the capacity of the urea cycle. In the second patient, symptoms developed after a 1-day fast. This history suggests a defect in fatty acid oxidation. During a prolonged fast, the brain relies on ketone bodies as an alternate source of energy, which are produced through fatty acid oxidation. The manifestations, pathophysiology, and