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Review Article

Inborn Errors of Metabolism: A Review Article

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Abstract:

Inborn metabolic errors are a diverse range of illnesses that can be inherited or result from natural mutation. Non-fulfillment of metabolic processes involved in the breakdown or storage of carbohydrates, fatty acids, or proteins causes several illnesses. Inborn errors of metabolism (IEM) are hereditary illnesses caused by mutations in genes that code for metabolism-related proteins. In one out of every 2000 newborns, a metabolic mistake is present. Carbohydrate metabolism, protein metabolism, fatty acid oxidation, and glycogen storage are all disrupted by IEM. Dietary nutrients are broken down in the body into glucose (the body's principal energy source) and other metabolic products, which are then eliminated. Patients with numerous glucose metabolism abnormalities present early in life (usually in the neonatal period). They might present with symptoms similar to Hypoglycemia, brady and tachycardias, hypothermia or hyperpyrexia, seizures, and hypotonia are several symptoms that septic newborns can have. In an emergency, a final diagnosis of inborn metabolic abnormalities is not a reasonable aim. However, because lab abnormalities in these patients may be transient, more blood should be drawn for further testing while they are still in the early stages. The PALS/ACLS method is used to administer vigorous resuscitation to these individuals. If you suspect a patient has inborn mistakes, don't give them anything by mouth (NBM). Because the emergency physician has no way of knowing which section of the metabolic pathway is malfunctioning, it's best to keep the patient from using his or her natural pathways for carbohydrate metabolism, metabolite clearance, or accessing nutrients of stored energy. It is therefore important for primary care providers to know how to recognize those conditions, manage them in the temporary while awaiting definitive diagnosis and refer them to the appropriate higher center for collaborative management of these patients.

Key words: Metabolism, Mutations, Hyperammonemia, Enzyme, Neonate

Introduction:

Inborn errors of metabolism are a heterogeneous group of disorders that may be inherited or may occur as the result of spontaneous mutation. These diseases involve Non-fulfilment of the metabolic pathways involved in either the breaking down or storage of carbohydrates or fatty acids or proteins. Although any given inborn error of metabolism is uncommon taken as a group, inborn errors occur in 1 in 2500 births, making them quite common. They can present at any age, and therefore, a working knowledge of these diseases, their manifestations, and their evaluation is critical for the emergency provider.[1-4]

Inborn errors of metabolism (IEM) are genetic conditions that block metabolic pathways involved in the breakdown of nutrients and the generation of energy. Perturbation of these metabolic pathways results in a spectrum of clinical findings affecting multiple organ systems. The diagnosis of IEM is challenging because the clinical presentation is often nonspecific; however, more IEM are now included in recommended newborn screening, which helps for early diagnosis. Therefore, knowledge of IEM has become essential for physicians. Although individual IEM are rare, the combined incidence is 1 out of every 1,500 births.[5]

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Etiology:

The inherited disorders caused by the mutations in genes coding for protein that work in metabolism are the Inborn errors of metabolism. Most of them are inherited as autosomal recessive. infrequently, they are autosomal dominant and X-linked. Environmental, epigenetic, and microbiome factors and additional genes are potential changing etiologic factors in those with inborn errors of metabolism.[5-8]

Epidemiology:

1 out of 2500 births have Inborn errors of metabolism. Because of their heterogeneity, different disorders have divergent epidemiologies, presentations, and heritabilities. Mitochondrial disorders are inherited from mother to 100% of her offspring, while other disorders may have variable penetrance or can be sex-linked. The disorder may cause complete ailment of the involved enzyme, or it may be partial or incomplete. Although neonatal birth screens identify many inborn errors of metabolism in advance, individual states and even individual hospitals have differing panels through which they screen. Neonatal screens may identify 8 to 50 different diseases, but woefully, there are thousands of diseases. Furthermore, screens may be falsely negative in children tested premature after birth (before they had the time to accumulate the measurable diagnostic metabolites) or in those who have received the transfusion. So, because of all these factors, although medical professionals often believe about inborn errors of metabolism as diseases of the neonatal period, 50% of all inborn errors are present outside of the neonatal period, and some are not diagnosed until maturity.[9]

Pathophysiology:

Inborn errors interrupt carbohydrate metabolism, protein metabolism, fatty acid oxidation, or glycogen storage. In the body, dietary substances are break-down into glucose (the primary energy source of the body) and other metabolic products that are eventually excreted. Glucose that is ingested but is more than what is needed is stored as glycogen in the liver and muscles for use in times of fasting. When the body needs glucose, it utilizes glycogen stores. When these stores are exhausted, the body will make new glucose from amino acids (gluconeogenesis) and then, finally, will use fatty acid oxidation to produce a substrate for the Kreb's cycle.[9-11]

Although there are comprehensive entries in Stat Pearls for specific inborn errors of metabolism, it is helpful to understand these diseases as a whole. Hypoglycemia is often caused by diseases that result in error of metabolism and breaking down food. Intoxication is caused by diseases that interfere with excretion of metabolites (i.e., hyperammonemia). Hypoglycemia and acidosis is caused by the diseases that interfere with fatty acid oxidation.

Clinical features:

Patients with severe errors in carbohydrate metabolism present prematurely (typically in the neonatal period) and catastrophically. Clinically, they can be very similar to septic neonates, with hypoglycemia, brady and tachydysrhythmias, hypothermia or hyperpyrexia, seizures, and poor tone. These children cannot metabolize food to fuel, and the prognosis with severe early involvement is bad. Patients with severe errors in excretion pathways will present classically with intoxication, with lethargy and altered mental status, seizures, vomiting, and vital sign abnormalities. They often have increased ammonia and other metabolites. Patients with errors in metabolic pathways involved in accessing stored energy may appear well for longer periods of time and can be asymptomatic as long as they have an underway intake of carbohydrates. However, the child develops a gastrointestinal illness should have a change in diet, or begin to forgo night feeds, he or she will be unable to use stored energy adequately and will present with hypoglycemia or seizures. These children may present with an illness that looks minor and short-lived, but appear quite ill.

Although all these presentations exists on a spectrum depending upon type of enzymes involved and degree, some common features are present in inborn errors of metabolism. The most common manefestations of these diseases taken as a whole is neurologic abnormalities, which occurs in about 80% of individuals. It includes developmental delay, loss of milestones, poor tone, poor suck, and seizure.

The second most usual presentation is related to gastrointestinal symptoms, including vomiting, hepatomegaly, food intolerance, diarrhea, food aversion, dehydration and exercise intolerance. More than half of the children have both neurological and gastrointestinal abnormalities. Hence, inborn errors of metabolism should be considered in the differential of any child with neurologic and/or gastrointestinal findings. Inborn errors should be considered in children with failure to thrive, formula changes and recurrent feeding issues, "reflux" or "gastroparesis," autonomic instability, or behavioral or learning issues.[9]

Newborn

IEM mainly present in the first month of life. Most of the times, the newborn will initially appear healthy because metabolites occurring in the IEM disorder have cleared via placental circulation during intrauterine period. Only after birth those metabolites accumulate; thus, a symptom-free period after birth is a vital component of the medical history.

Symptoms in newborns are typically nonspecific, such as lethargy, poor feeding, vomiting, abnormal breathing, seizures, and/or hypotonia. Although these signs also suggest infection (including sepsis), which is more common, IEM must be considered in the differential diagnosis. Additional findings that should raise concern about the possibility of an IEM disorder are unexplained hypoglycemia metabolic acidosis, constitutional liver dysfunction, and encephalopathy.[12]

Children:

Most conditions that present in the newborn period can present during childhood in a similar or less severe manner and in some cases are linked with dysmorphic physical examination findings.[13-15] Two of the most wellknown examples are lysosomal storage disorders, Hunter syndrome and Hurler syndrome.[16-17] The dysmorphic features may not present at birth, but they become more pronounced over time as the storage molecule accumulates.

Adolescents and Adults:

Primary care physicians occasionally encounter IEM in adolescents and adults. Some of the children with IEM are living longer because of new treatments and a better understanding of how to avoid metabolic decompensation (e.g., avoiding high-protein diets in organic acidemia and urea cycle disorders). Some IEM also have their onset in adults, for example, adult-onset lysosomal storage disorders. Residual enzyme activity is seen in patients with IEM, that allows for slow accumulation of toxic molecules over time, and symptoms may not appear until adulthood. Some of these disorders (e.g., Gaucher disease) can be treated with enzyme replacement therapy.[18]

Screening:

Definitive diagnosis of inborn errors of metabolism is not a sensible goal in an emergency setting. However, because lab abnormalities in these patients may be temporary, it is important to draw extra blood for future testing at the time of initial presentation. Although a definitive specific diagnosis is not likely in an emergency department, some labs are helpful in screening for these diseases. Most children with inborn errors of metabolism will have a raised lactate level, hyperammonemia, hypoglycemia, or acidosis on blood testing, or ketonuria / elevated urinary reducing substances on urine testing. These tests are therefore, used as a screen for possible inborn errors, with the extra tubes that are saved for further serum amino-acid and organic-acid testing should these tests be positive.

Preconception:

The first opportunity for addressing IEM occurs with testing of asymptomatic future parents. Some population have increased carrier rates for IEM, and preconception screening has been shown to decrease disease prevalence. Carrier testing was first started in the Ashkenazi (Eastern European) Jewish population in the early 1970s with preconception screening for carriers of Tay-Sachs disease.[19-20] With the advent of carrier screening, the incidence of Tay-Sachs disease decreased by 90% between 1970 and 1993 in the Jewish populations of North America. The American College of Obstetricians and Gynecologists (ACOG) and the American College of Medical Genetics and Genomics (ACMG) have expanded the list of recommended carrier testing for IEM beyond TaySachs disease in the Ashkenazi Jewish population.[21-23]

Newborn:

The screening of IEM disorders began in the 1960s with Dr. Robert Guthrie who developed a screening test for phenylketonuria (PKU) from a blood spot ; due to early knowledge of the disorder treatment of PKU with diet restriction of the amino acid phenylalanine was possible .9 Expanded newborn screening beyond PKU has occurred largely due to introduction of tandem mass spectrometry, which allows for testing of multiple metabolic conditions from a single blood spot.10,11 Sensitivity for newborn screening is 99.9% using tandem mass spectrometry , and specificities range from 99.9% to 99.99%. Because of the low prevalence of these conditions, however, positive predictive values range from 26% to 37%.[24-25]

Treatment:

The initial treatment in these patients is aggressive resuscitation via the PALS/ACLS algorithm, So do not give anything by mouth (NPO) to patients in whom inborn errors are suspected. Since the emergency provider cannot know which part of the metabolic pathway is deranged, it is wise to prevent the patient from utilizing his or her native pathways for, clearance of metabolites, carbohydrate metabolism, or accessing of stored energy. Therefore, the patient should receive pure substrate (glucose) at a volume that prevents the need for the patient to break down glycogen or fatty acids. This should be accomplished with 10% dextrose solution at a one and a half maintenance rate. The patients may need to provide insulin (0.05 U/kg/hour to 0.2 U/kg/hour) to treat hyperglycemia. Patients with raised ammonia may be given nitrogen scavengers such as sodium benzoate or sodium phenylacetate, but patients require dialysis with ammonia levels greater than 600. Most of the patients who are ill with suspected inborn errors of metabolism will require monitoring in an intensive care unit setting.

Infants, children and adolescents with IEM who appear normal can succumb to life-threatening conditions. Appropriate acute illness protocol (see Table 4) and specific supportive therapies are needed to assure the patient's survival. Many patients will require circulatory and respiratory support. Most of them will require rehydration, correction of electrolyte imbalance and even treatment of overwhelming infection from opportunistic organisms that uncorrected can lead to persistent catabolic state and failure of definitive therapeutic intervention.[26]

Nutrition

Whatever may be the IEM disease condition, addressing the nutritional requirements of the patient is very important. Most of the patients who are hemodynamically unstable or septic may have to have nothing by mouth (NPO) initially for first day or two to temporarily eliminate exposure to or reduce the incidence of toxic metabolites in the system. Total parenteral nutrition (TPN) is preferred in those cases wherein effective enteral nutrition is not acceptable due to intestinal intolerance, high energy or high glucose requirements or the introduction of invasive techniques are needed for immediate detoxification. If the patient is stable, enteral or oral nutrition is encouraged with one of these four types of diet: normal, low-protein, carbohydrate-restricted, high-glucose with or without lipid restriction.[27]

CNS deterioration

Children and infant with IEM can suffer metabolic encephalopathy and these include: MSUD, BCOAs, and UCD. These patients can develop overhydration, cerebral edema and acute protein malnutrition if not properly managed. Careful monitoring of blood glucose, lactate, calcium, ammonia levels are imperative to know when to implement correction of the electrolyte and acid-base imbalance. Specific therapies such as insulin administration may be used to suppress severe catabolism or infusion of massive doses of specific vitamins may be essential for vitamin-dependent disorders.[28]

In the presence of intractable seizures, vitamin responsive IEM must be considered. Giving certain vitamins like pyridoxine, biotin, thiamine, folinic acid and vitamin K may be life-saving and warranted to alleviate some of the symptoms.

Liver failure

Many IEM conditions presenting with jaundice, coagulopathy, hepatocellular necrosis with elevated levels of serum transaminases, hypoglycemia, ascites and generalized edema results in liver failure. The disorders include: fructosemia, galactosemia, tyrosinemia type 1, neonatal hemochromatosis, respiratory chain disorders and transaldolase deficiency. These abnormalities are most of the times associated with mellituria, hyperammonemia, hyperlactatemia, hypoglycemia, hypertyrosinemia and hypermethioninemia secondary to advance hepatocellular disease.

Cardiac failure:

Failure of heart and dilated hypertrophic cardiomyopathy can be the presenting symptom of the metabolic disorders associated with FAO disorders, mitochondrial disorders or Pompe disease. These patients show hypotonia, muscle weakness and failure to thrive. IEMs involving long chain FAO can show arrhythmias and conduction defects that may lead to cardiac arrest and death.

Management of chronic problems:

Almost half of patients with IEM presents with delayed onset of symptoms. The symptom-free period can last for months or even years extending into adolescence or adulthood. These periods of normalcy may be punctuated with acute episodes of attacks most of the times precipitated by an intercurrent event related to protein intake, prolonged fasting, prolonged exercise or any condition that exacerbates protein catabolism. That is why it is imperative to coordinate care with the metabolic specialist to anticipate these crisis situations when they do occur.[27]

Conclusion:

Clinical outcome of children with IEM depends on multiple factors. These include type of the disorder, ability to make the diagnosis early, severity of the underlying metabolic defect, availability of specific adequate treatment options and appropriate institution of the definitive therapeutic intervention. That is why it is important for primary care providers to know how to recognize those conditions, manage them in the interim while awaiting definitive diagnosis and refer them to the appropriate higher center for collaborative management of these patients. Managing the patients with inborn errors of metabolism is extremely complex and challenging. As there is no cure, the disorders are best managed by an inter professional team that includes pharmacists, nurses, therapists, dietitians, and social workers.

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