Review Article

Treatment strategies for acute metabolic disorders in neonates

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ABSTRACT

Acute metabolic emergencies in neonates represent a challenge to the medical and nursing staff. If not treated optimally, these disorders are associated with poor outcome. Early diagnosis, supportive therapy and specific measures addressing the derranged metabolic process are the gold standards for favorable results. This review highlights treatment strategies for Inborn Errors of Metabolism (IEM) presenting in the neonatal period.

Key words: Inborn errors, Metabolism, Neonate.

Acute metabolic disorders often manifest with life threatening episodes in the neonatal period. [1-7]. The advances in technology, especially with the utilization of tandem mass spectroscopy in the screening and diagnosis of metabolic disorders, mandate general pediatricians to acquire basic knowledge and experience that help them to effectively manage these growing disorders [8-14]. Early detection of potentially treatable inborn errors of metabolism (IEM) cannot be overemphasized [15, 16]. The prognosis of IEM is dictated by the initial treatment measures put in place in the early phase of clinical presentation [17-20]. Having a practical and a scientific sound approach dose not only facilitate the clinical diagnosis and management but also improve the outcome. This article starts where the previous related one in this journal ends [21]. It deals with what to do when a diagnosis is suspected and later when it is confirmed. Therefore, the aim of this review is to outline the principals of treatment measures that can be applied comfortably at a general pediatric setting.

Treatment strategies

Protein disorders such as urea cycle defects [22], maple syrup urine disease [23], and organic aciduria [24-26] account for the majority of sick neonates with IEM. Basic measures such as discontinuation of protein intake, supportive therapy and removal of toxic metabolites may improve the outcome of these

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disorders [1, 2, 4, 5].

Energy insufficiency disorders such as hyperinsulinism, and glycogen storage diseases contribute to the adverse outcome of IEM in neonates [27-29]. Treatment strategies for this group include provision of high calories that fixes most of the unwanted metabolic effects, promote anabolism and inhibit catabolism. These strategies are listed in six measures (Table 1)

Table 1 - Treatment strategies for acute metabolic disorders

Strategy	Example
Supportive therapy	Cardio respiratory support
Removal of toxic metabolite	Ammonia, leucine
Provision of optimum vitamins and cofactors	Cobalamin, thiamine
Specific drugs and enzyme replacement therapy for IEM	Carnitine, diazoxide
Special dietary management	Low protein, galactose free formula

IEM - inborn errors of metabolism.

1-Supportive therapy

The vast majority of neonates with acute IEM present to medical facilities sick and often unstable. These patients need admission to high dependency or intensive care unit where experienced staff, who are familiar with management of acutely sick patients, are available. The priority step is to secure a patent airway (Table 2). Assisted ventilation may occasionally be needed should respiratory effort becomes inadequate. Two peripheral intravenous accesses should be inserted. A central venous line is necessary. Hypovolemic shock, if present, is treated by intravenous boluses of isotonic saline. Fluids and electrolytes are closely observed and corrected according to the clinical and laboratory findings. This is achieved by careful measurement of fluid balance and frequent monitoring of serum electrolytes. The maintenance fluid of choice is usually Dextrose 10% with added salts. Insulin infusion, 0.05 unit/ kg/ hour, may be needed should hyperglycemia occurs. This will maximize the calories, push glucose into cells, and prevent osmotic diuresis. High calories promote anabolic process and inhibit catabolism leading to decrease load on the affected metabolic pathways with possible decrease in accumulation of harmful abnormal metabolites. Discontinuation of protein intake is a preventive measure as most of IEM presenting with decompensation early in life are protein metabolic disorders. Cardiac support in terms of starting positive intropes helps patients with circulatory compromise. Correction of acidosis by intravenous sodium bicarbonate infusion enhances cellular metabolic functions and decreases the impact of metabolic decompensation particularly on the central nervous system and the contractility of the heart [30], Correction of hypothermia and treatment of cerebral edema by manitol are important measures to stabilize patients with IEM.

Acute metabolic decompensation may occasionally be induced by sepsis. Both sepsis and IEM may show non specific symptoms early in the course of the disease. Sepsis is well known to be associated with certain IEM such as classic galactosemia [31]. So, it is sometimes difficult to know whether sepsis is a cause or an effect of IEM especially early in the course of the disease when a definitive diagnosis is not reached. For all these reasons covering neonates with broad spectrum antibiotics is essential if IEM is suspected.

2-Removal of toxic metabolites

Removal of abnormally accumulated toxic metabolites is an important strategy in the management of neonates with acute metabolic decompensation. Urea cycle defects lead to accumulation of ammonia in the blood [32]. Ammonia is normally converted to urea in a cascade of biochemical reactions [33]. While ammonia is lipid soluble, urea is water soluble and accordingly is excreted through the kidneys. High level of serum ammonia is toxic to the body especially the central nervous system leading to acute encephalopathy, seizures, and cerebral edema [34]. Early measurement of serum ammonia in neonates with possible metabolic disease is crucial [35]. Management of hyperammonemia in neonates with urea cycle defects is summarized in Table 5. Management of hyperammonemia requires a multidsplinary approach with involvement of all relevant health professionals such as intensivist, nephrologist, pediatric surgeon, pharmacist, laboratory staff, dietician, and social worker [36]. Supportive measures as outlined above are the corner stone in the treatment. When serum ammonia level is above 200 µmol/l ammonia lowering medications are commenced [37]. These include intravenous infusion of arginine, sodium benzoate and sodium phenylbuturate. Dialysis is indicated when ammonia level is above 400 µmol/l [32-38]. Low protein special formula is started when the patient is stable and ammonia has normalized.

Maple syrup urine disease (MSUD) is caused by deficiency of the enzyme branched- chain α ketoacid dehydrogenase [23, 39]. The hallmark of this disorder is accumulation of the amino acid leucine. Abnormal accumulation of leucine is toxic to the brain leading to acute encephalopathy and cerebral edema [23]. Assay of serum amino acid early in the course of the disease is usually diagnostic of this condition. If high serum leucine does not respond to the general supportive measures, dialysis is indicated to remove leucine from blood [23].

Table 2 - Supportive therapy for acute metabolic disorders

Therapeutic measure	Example
Respiratory support	Oxygen, ventilation
Circulatory support	Fluids, inotropes
Correction of acidosis	Sodium bicarbonate infusion
Fluid and electrolyte correction	Adjust type of fluids according to electrolyte level
Promote anabolism	Provide high calories (Dextrose 10% or more)
Treat hyperglycemia	Insulin infusion
Cover with antibiotics	Broad spectrum antibiotics

3-Provision of optimum vitamins and cofactors

A number of deficient enzymes implicated in the pathogenesis of IEM are catalyzed by certain vitamins and cofactors. Supplying patients with these cofactors augment and enhance the enzyme residual activity [1-4]. Some variants of methylmalonic aciduria respond to vitamin B 12 while few patients with MSUD improve when given thiamin [1-3]. Table 3 shows vitamins and cofactors used in the treatment of IEM.

Table 3 - Vitamins and cofactors used in acute metabolic disorders

Vitamin or cofactor	Disorder
Thiamine	Maple syrup urine disease
Riboflavin	Gluteric aciduria type 2
Vitamin B12	Methylmalonic aciduria
Biotin	Proprionic aciduria
Vitamin B6	Homocystinuria

4-Specific drugs and enzyme replacement therapy for IEM

Some IEM presenting in the neonatal period have specific drug therapy. Table 4 shows the drugs used in the treatment of these IEM. The role of arginine, sodium benzoate, and sodium phenylbuturate in treating hyperammonemia is already discussed. Congenital hyperinsulinism (CH) is a potentially treatable condition [40]. Newborn babies with CH present with persistent hypoglycemia [41]. Their glucose requirement is above 12 mg/kg/minutes [42]. The principal of treating CH is to provide adequate carbohydrate supply and to inhibit insulin release by pancreatic β cells. Neonates with CH respond to glucagon, octreotide, and diazoxide [40-44]. Near total pancreatectomy is indicated when medical treatment fails [42-44].

Tyrosinemia type 1 is caused by deficiency of the enzyme fumaryl acetoacetase [45]. This leads to accumulation of tyrosine and the hepatotoxic metabolite, succenylacetone that leads to acute porphyria like crisis, as well as liver and kidney damage [46]. 2-nitro-4-trifluoromethylbenzyl 1, 3 cyclohexanedione (NTBC) inhibits the enzyme 4-hydroxyphenylpyruvate dioxygenase, which is required in an early step in the catabolism of tyrosine, thus preventing the formation of succenylacetone [45-47]. If started shortly after birth, NTBC prevents development of progressive liver disease, and possibly hepatoma [45, 46].

Oxidation of fatty acid takes place inside the mitochondria [48]. To enter the mitochondria, long chain fatty acids need to be bound to carnitine which acts as a vehicle [49-51]. Carnitine itself enters cells via the plasma membrane [51]. Primary carnitine deficiency results from carnitine transporter defect which is an autosomal recessive condition that presents with cardiomyopathy in the neonatal period [51-53]. This condition responds well to carnitine replacement therapy and represents one of the few treatable causes of cardiomyopathy in neonates [51-53]. Secondary carnitine deficiency that may require replacement therapy is associated with different types of fatty acid oxidation defects and some of the organic aciduria [51, 52].

Enzyme replacement therapy was a breakthrough in the treatment of some of IEM like Pompe disease [54, 55]. The deficient enzyme in Pompe disease is lysosomal acid maltase
(α glucosidase). These patients may show evidence of cardiomyopathy and hypotonia early in the neonatal period. Enzyme replacement therapy for these patients has shown remarkable effects with improvement in cardiomyopathy, hypotonia and developmental milestones [54-56].

Table 4 - Specific drugs used in treatment of acute metabolic disorders

Drug	Disorder
NTBC	Tyrosinemia
Carnitine	Carnitine transporter defect, organic aciduria
Betaine	Homocystinuria
Carglumic acid	N-acetylglutamate synthetase deficiency
Sodium benzoate	Urea cycle defects
Sodium phenylbutyrate	Urea cycle defects
Arginine	Urea cycle defects
Glucagon	Hyperinsulinism
Octreotide	Hyperinsulinism
Diazoxide	Hyperinsulinism

NTBC - 2-nitro-4-trifluoromethylbenzyl 1, 3 cyclohexanedione

5- Diet Management

As most of IEM result in harmful accumulation of a substrate and deficiency of a product, the principal of diet management of these disorders is to restrict the intake of the accumulated substance and to supply the deficient product [57]. Table 6 shows some special diet formula used in the treatment of IEM presenting in the neonatal period. The hallmark of treatment of classic galactosemia is to restrict galactose intake by introducing lactose free formula [1, 2]. Likewise, patients with tyrosinemia benefit from low tyrosine formula in addition to NTBC therapy [1, 3]. Dietary management of urea cycle defects, MSUD, and organic acidurias involves restriction of protein intake including the offending amino acid, that is available in special milk formulas [57]. Patients with fatty acid oxidation defects develop hypoglycemia when they are exposed to stressful conditions such as prolonged fasting, infections, or anesthesia [57]. The principal of dietary management of fatty acid oxidation defects entails avoiding prolonged fasting and supplying patients with adequate carbohydrate intake during acute illnesses [1, 2, 57].

In conclusion, most of the IEM presenting in the neonatal period respond to treatment if the diagnosis is thought of early in the course of the disease and appropriate treatment strategies were adhered to.

Table 5 - Treatment of hyperammonemia

Therapeutic strategy	Details
Supportive therapy	Cardio respiratory support, ventilation, correction of fluids, electrolytes, and acidosis.
Promote acidosis	Discontinue protein intake, intravenous 10% Dextrose, and intravenous intralipids.
Ammonia lowering drugs	If ammonia > 200 µmol/l, start intravenous infusion of arginine, Sodium benzoate, and sodium phenylbutyrate.
Carglumic acid	If acetylglutamate synthetase deficiency is suspected.
Dialysis	If ammonia > 400 µmol/l
Low protein formula	Start when ammonia is normal or near normal

Table 6 - Special dietary formula for acute metabolic disorders in the neonatal period

Special formula	Disorder
Low tyrosine	Tyrosinemia
Low methionine	Homocystinuria
Low leucine, isoleucine, and valine	Maple syrup urine disease
Low isoleucine, valine, methionine, and threonine	propionic/ methylmalonic aciduria
Low protein	Urea cycle defects
Galactose free	Galactosemia
Frequent glucose and glucose polymers	Glycogen storage disease

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