

ACUTE ENCEPHALOPATHY IN CHILDREN WITH INBORN ERRORS OF METABOLISM (A PRACTICAL APPROACH)

ENCEPHALOPATY AKUT PADA ANAK DENGAN KELAINAN METABOLISME BAWAAN (PENDEKATAN PRAKTIS)

Anik Puryatni*, Tom J. de Koning**

*Division of Nutrition and Metabolic diseases, Department of Pediatrics, Saiful Anwar General Hospital, Medical Faculty of Brawijaya University

**Department of Pediatrics Metabolic diseases, Wilhelmina Children's Hospital, University Medical Centre of Utrecht, Netherlands

ABSTRACT

Acute encephalopathy is a not a common, but a potential emergency situation in newborns and young children. If the encephalopathy is not caused by asphyxia or infections of the brain, rare inborn errors of metabolism need to be considered. An acute encephalopathy due to an inborn error can occur in newborns, young infants, or even in childhood and is not always easily recognized because more subtle presentations can occur. In this article we will give a practical guideline to the diagnostic approach of metabolic diseases presenting with acute neurological symptoms with an emphasis on treatable disorders and the application in developing countries with limited diagnostic resources. The first step in the evaluation of patient with a possible metabolic disease is to categorise the clinical appearance of the patient in one of the following clinical categories: Hypoglycemia phenotype; Intoxication phenotype; Neurotransmitter defect phenotype; and Cellular energy metabolism defect phenotype. Second, combine this clinical classification with your physical examination and the result of routine laboratory investigations and this can lead to suspected diagnosis of metabolic disorders. Prompt recognition and treatment are important, because an acute metabolic encephalopathy can irreversible and interruption of normal neural activity in the developing brain can have a long-lasting effect on psychomotor development. Delay in diagnosis and treatment may thus result in acute metabolic decompensation, progressive neurologic injury, or even death.

Key words: acute encephalopathy, inborn error metabolisme

INTRODUCTION

Acute encephalopathy is condition of acute global cerebral dysfunction resulting in altered consciousness, behavior changes, or seizures that is not due to a primary structural brain disease (e.g. tumor or hemorrhage) or infection (1,2). Metabolic disorders are only one of the causes of acute encephalopathy and in the early stages it can be difficult to establish the diagnosis. Nevertheless, early diagnose and prompt treatment are important to do so given the limited amount of time to protect the brain from irreversible damage (2,3).

Acute encephalopathy is a common and potentially medical emergency in patients with inborn errors of metabolism (IEM) (2). Some of these disorders are treatable and require the emergency removal of the toxin by special diets, extracorporeal procedures, cleansing drugs or vitamins (2,3).

The presentation of a metabolic disease can be in the newborn, infant, or in childhood and the symptoms can be overwhelming in severe disease or may be more subtle or intermittent and not easily recognized (4,5,6,7). In infants and children the

symptoms are indeed precipitated by metabolic stress such as infections, fasting or surgery and In the newborn this symptoms usually start after several days when feeding started and toxic metabolites are not longer cleared by the maternal circulation (4,5,6). Prompt recognition and treatment are important, because the encephalopathy is often reversible early in the disease process, but prolonged interruption of neural activity in the developing brain can have a long-lasting effect (6,7). Individual IEM are rare disorders, most having an incidence of less than 1 per 100.000 births. However, when considered collectively, the combined/cumulative incidence may approach 1 in 800 to 2500 births (8,9).

Most inborn errors of metabolism are inherited as autosomal recessive conditions, some follow an x-linked recessive genetic pattern and in rare instances inheritance can be maternal or autosomal dominant (7,9). Optimal outcome for children with IEM depends upon timely recognition of the signs and symptoms of metabolic disease, and prompt evaluation and referral to a center familiar with the management of these disorders. Delay in diagnosis may have serious consequences resulting in acute metabolic decompensation, progressive neurologic injury, or death (10). The diagnosis and treatment of acute

metabolic disorders obviously can be very complex, but in this article we will give a practical guideline to the diagnosis of IEM presenting with acute neurological symptoms in newborn and children. We will focus on those disorders that can be diagnosed and treated by simple means and therefore this guideline is applicable in developing countries like in Indonesia. We will limit this article to those disorders where the acute symptoms of the central nerve system are predominant and are treatable by easy means and will not discuss acute metabolic disorders presenting with acute cardiac or hepatic signs or those disorders with a slow progressive phenotype like the lysosomal storage disorders.

Diagnosing Children with An Acute Metabolic Encephalopathy

Unfortunately, the symptoms of IEM in children are usually non specific and resemble more common causes of global brain dysfunction such as meningitis and encephalitis. In a typical case within a few hours or weeks after birth, a previously healthy neonate may begin to show signs of the underlying metabolic disorder. The presenting symptoms typically are lethargy, decreased feeding, vomiting, tachypnea, decreased perfusion, seizures, and can progress to stupor and coma with progressive abnormalities of tone (hypotonia, hypertonia), posture (fisting, opisthotonus), and movements (tongue-thrusting, lip-smacking, myoclonic jerks) (11,12).

Older infants with inborn errors of metabolism may demonstrate paroxysmal stupor, lethargy, emesis, failure to thrive, or organomegaly. Additional neurologic findings of neurometabolic disorders are acquired macrocephaly or microcephaly, hypotonia, hypertonia/spasticity, seizures, and movement disorders (11).

In toddlers and preschool-age children, the features of metabolic disorders include stagnation or loss of cognitive and motor milestones; loss of expressive language skills; progressive deficits in attention, focus, and concentration; and other behavioral changes (11).

Diagnostic Steps

The first step in the evaluation of a patient with a possible metabolic disease is to describe the clinical appearance and put the symptoms of your patient in one of the clinical categories mentioned below (13).

1. Hypoglycemia phenotype
2. Intoxication phenotype
3. Neurotransmitter defect phenotype
4. Cellular energy metabolism defect phenotype

Second to this clinical classification is to use routine diagnostic tests to further discriminate a possible IEM. Routine biochemical screening tests should include the testing of blood gas, glucose, lactate and ammonia, because an elevated plasma ammonia level, hypoglycemia, elevated lactate and

metabolic acidosis or respiratory alkalosis are all suggestive of inborn errors of metabolism. The routine laboratory studies that should be obtained for an infant or children with a suspected inborn error of metabolism are:

- Complete blood count with differential
- Blood gases
- Serum electrolyte
- Blood glucose and CSF glucose
- Plasma ammonia
- Plasma lactate

One should also be aware of the limitations of these routine diagnostic tests. Ammonia is difficult (and expensive) to analyze and the levels of ammonia will also rise in every anaerobic condition such as difficulties with drawing the blood, and not collecting samples on ice. Exactly, the same is true for lactate of which the levels will also rise in every anaerobic condition such as hypovolemic shock and cardiac failure. When it is impossible to analyze ammonia or lactate, the blood gas can give you some information. A metabolic acidosis is usually present when lactate is high (usually above 5-6 mmol/l) and a respiratory alkalosis is usually present with an isolated elevation of ammonia (usually above 200 $\mu\text{mol/L}$) (13).

The third step in the diagnostic procedure is to combine the clinical classification with your lab results and some clues from the patient history and physical examination to strengthen the suspicion of a metabolic disorder. It is important to note that completely normal results of routine biochemical tests are also very informative, normal results of diagnostic blood tests are always seen in those IEM restricted to the brain compartment. So normal results of routine diagnostic tests does not rule out a IEM.

A patient with a hypoglycemia phenotype

The symptoms of patients with a hypoglycemia due to an IEM are identical to other causes of hypoglycemia and should be easy to recognize by all pediatricians. Patients with hypoglycemia present with lethargy, apathy, feeding problems, decrease consciousness and eventually seizures. When there are no risk factors such as prematurity, dysmaturity, maternal diabetes or a serious infection, the symptoms of a hypoglycemia in this patient can be caused by a metabolic disorder.

When your patient has a hypoglycemia, first evaluate the time of the last meal the patient had before the hypoglycemia occurred. When this time was relatively short, within 1-2 hours after the last meal and the hypoglycemias come unpredictable, this is very suggestive of hyperinsulinism. If the hypoglycemia occur after some hours, for instance after 3-5 hours, this is suggestive of glycogen storage disorder, in particular type 1 glycogen storage disorder (14). The symptoms are frequently seen in the patients when the frequency of breastfeeding

or/formula is reduced when newborns are 4-5 months of age. When the hypoglycemia occurs after a longer feeding pause or after a night fasting, during intercurrent infections or after a period of not eating well, this is very suggestive for disorder of gluconeogenesis or fatty acid oxidation (15). Secondly, examine the liver and check whether it is enlarged on physical examination. The liver is large in glycogen storage diseases, impairments of gluconeogenesis, and is frequently enlarged in fatty acid oxidation disorders (14,15). Finally combine the data above with the blood results. When the patient does not only have a hypoglycemia, but also an increased plasma lactate, this indicates a GSD or gluconeogenesis defect. In children with fatty acid oxidation disorders, the ketones in urine at the time of the hypoglycemia will also be low and this could be of help in diagnosing these patients (14,15).

A patient with an intoxication phenotype

The symptoms of an endogenous intoxication are not different from other intoxications, such as alcohol intoxication. Nausea, vomiting, anorexia, dehydration, altered consciousness, muscle tone impairment, movement disorders (ataxia and dystonia), convulsions and coma are all symptoms of intoxication. In the beginning, the symptoms of gastro intestinal complaints predominate and sometimes an intestinal obstruction or anatomical abnormality is suspected. When the endogenous intoxication persists, neurological symptoms will occur in combination with signs of other organ dysfunction such as liver dysfunction, alopecia, cardiomyopathy, pancreatitis, and bone marrow failure.

When the patient has a clinical phenotype of intoxication and the lab tests show a high lactate and ammonia, this is very suggestive of an organic acidemia (16). When the lab tests show mainly an increased ammonia, a urea cycle defect is more likely. In both groups of disorders the liver is enlarged. The diagnosis of a urea cycle defect is further supported by presence of a respiratory alkalosis, combined with (highly) elevated transaminases (17). Besides the signs of intoxication, brain edema can be present and sometimes focal neurological abnormalities are present. In contrast, an organic acidemia can present with a normal blood gas and the lactate and ammonia are not necessarily elevated to the same extent. It can be very confusing, looking at the literature of organic acid disorders, but the denominations acidemia and aciduria are both used and are related to the fact that in the past the abnormal metabolites were detected either in blood or urine.

A patient with a neurotransmitter defect phenotype

The clinical symptoms in this category are limited to the central nervous system and patients present with convulsions, changes of consciousness,

movement disorders, abnormal muscle tone and coma. The complaints not necessarily present directly after birth, but can occur until after first years of life. The symptoms indicate a serious dysfunction of the brain, but all routine lab tests show normal results. Usually, a lumbar puncture has already been performed to exclude a meningitis or encephalitis showing no signs of infection. It is tempting to start with brain imaging or EEG examination, but these diagnostic tests contribute little to the diagnosis of easy to treat IEM. Therefore your approach should better be aimed at treatable disorders, such as maple syrup urine disease (MSUD), the vitamin dependent forms of epilepsy, and for children where the symptoms start somewhat later, glucose transporter deficiency, and late-onset non ketotic hyperglycinemia (NKH) (18,19,20). We will focus on a limited number of disorders that are diagnosed and treated by simple means. One should realize however, that besides the above mentioned disorders, many IEM can present with neonatal seizures, but treatment options are usually limited and the diagnostic process can be extensive. Among these disorders are patients with striking dysmorphism, such as patients with the 'Zellweger syndrome', congenital disorders of glycosylation (CDG syndrome), and Menke's disease. However, the findings on physical examination are guiding in the diagnostic process and sometimes very specific, but unfortunately as in the majority of causes of neonatal seizures, treatment options are limited.

A patient with disturbance in cellular energy metabolism phenotype

Children in this category usually are more difficult to categorize than children in the other three groups. Clinically these children have complaints of multiple organs such as the brain, heart, skeletal muscle, liver, kidneys, and gastrointestinal tract. For this clinical presentation the group of mitochondrial encephalopathy stands model. The symptoms can be present shortly after birth with hypotonia, convulsions, muscle weakness, cardiomyopathy, and multi organ failure. However the complaints can arise also later with regression of the development, hypotonia, feeding problems, and deterioration of clinical symptoms after infection or vaccinations. Frequently the plasma lactate is increased and sometimes it is very high. The determination of lactate/pyruvate ratio's and keton body's ratio, combined with metabolic test of blood and urine can support a specific disorder in the group of cellular energy defects. Unfortunately lactate is not elevated in all patients, not even in cerebrospinal fluid. It is important to realize this and therefore normal lactate concentrations are not a reason to reject this diagnostic group. The diagnosis should be suspected on the basis of the clinical findings and additional investigations. Applying specific diagnosis criteria for this group of children may further contribute to the suspicion on

mitochondrial disease (21). Mitochondrial diseases, or cytopathies, should be considered in the differential diagnosis when there are these unexplained features, especially when these occur in combination (see in table 2) (22)

Table 1. Problems Associated with Mitochondrial Cytopathies (22)

Organ System	Possible Problems
Brain	Developmental delays, mental retardation, dementia, seizures, neuro-psychiatric disturbances, atypical cerebral palsy, migraines, strokes
Nerves	Weakness (which may be intermittent), neuropathic pain, absent reflexes, gastrointestinal problem (gastroesophageal reflux, delayed gastric emptying, constipation, pseudo-obstruction), fainting, absent or excessive sweating resulting in temperature regulation problems
Muscles	Weakness, hypotonia, cramping, muscle pain
Kidneys	Proximal renal tubular wasting resulting in loss of protein, magnesium, phosphorous, calcium and other electrolytes
Heart	Cardiac conduction defects (heart blocks), cardiomyopathy
Liver	Hypoglycemia, liver failure
Eyes	Visual loss and blindness
Ears	Hearing loss and deafness
Pancreas	Diabetes and exocrine pancreatic failure (inability to make digestive enzymes)
Systemic	Failure to gain weight, short stature, fatigue, respiratory problems including intermittent air hunger

Table 2. The suspicion of a metabolic disorder from the clinical classification of acute encephalopathy phenotype (14)

Phenotype	clinical sign	Metabolic disorder
Hypoglycemia	shortly after meal, unforeseeable, raised glucose need	Hyperinsulinism
	after some hours meal, liver enlargement increased lactate	Glycogen storage disease : GSD type 1, GSD type 3
	After fasting night, infection, liver enlargement increased lactate	Fructose 1,6 biphosphatase deficiency
	After fasting night, infection, liver enlargement absent ketone urine	Disorders of fatty acid oxidation: MCAD, LCHAD, VLCAD
intoxication	liver enlargement Increased lactate and ammonia	Organic acidemia (Propionic academia, Methylmalonic academia, Isovaleric academia)
	Liver enlargement increased ammonia	Urea Cycle Defect
neurotransmitter defect	Focus in treatable disorder	<ul style="list-style-type: none"> - MSUD (Maple Syrup Urine Disease) - Pyridoxine-responsive seizures - Pyridoxal phosphate-responsive seizures - glucose transporter (GLUT1) deficiency Disorders of glucose transport - "Late onset" non-ketotic hyperglycinemia
defect energy cellular	Involve several organs, increased lactate	<ul style="list-style-type: none"> - pyruvate oxidation defect <ul style="list-style-type: none"> o PDHC deficiency - citric acid cycle defect - respiratory chain defect complex I, II, III, IV, V - mtDNA depletion syndrome

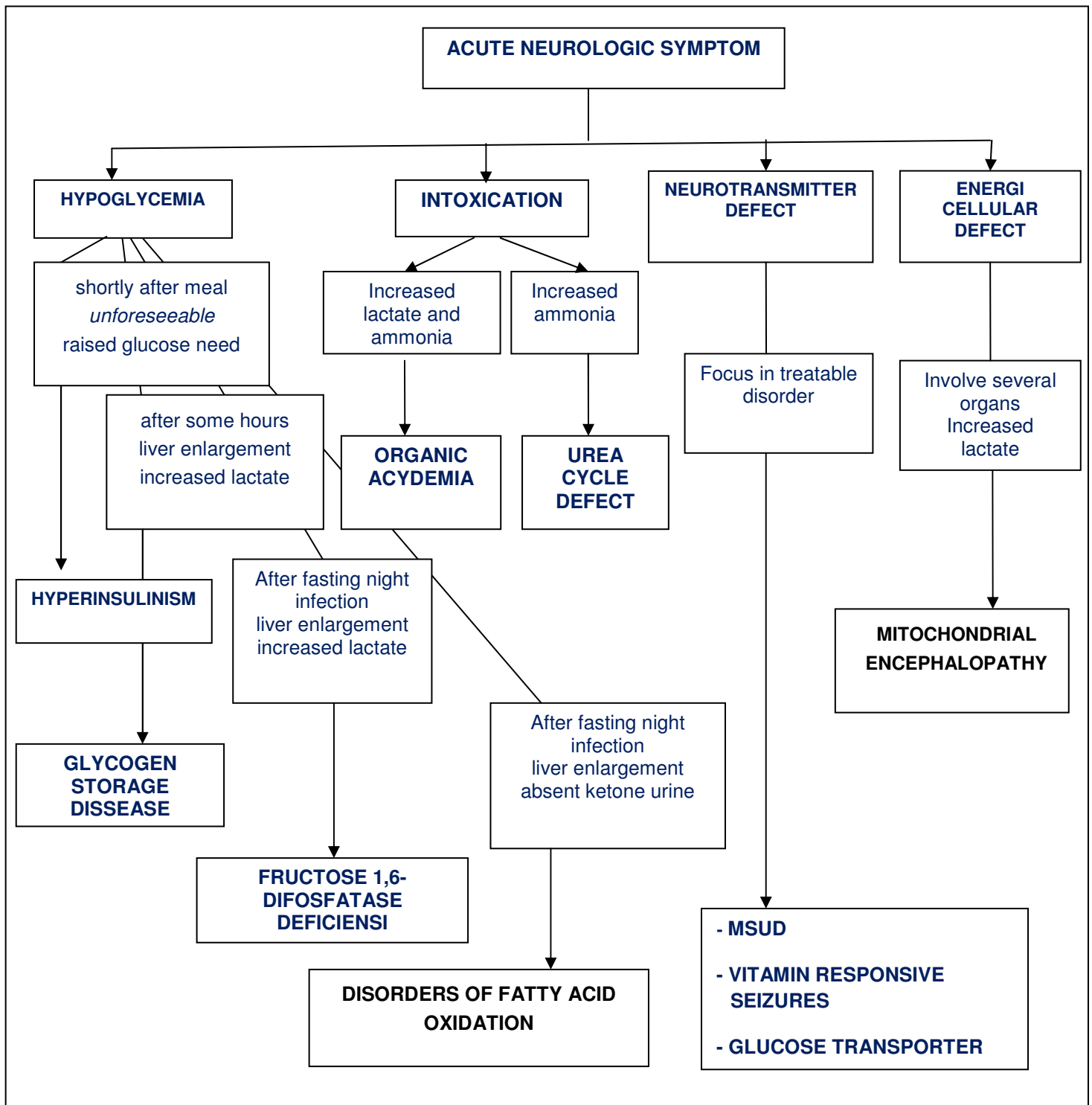


Figure 1. Flowchart for differentiation diagnosis of conditions associated with acute metabolic encephalopathy (created with permission with De Koning TJ) (14).

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