Inborn Errors of metabolism in Infancy

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Clinical Manifestations

Acute metabolic encephalopathy

Metabolic acidosis

Hyperammonemia

Hypoglycemia

Jaundice or hepatic dysfunction

Dysmorphyism

Acute metabolic encephalopathy

Toxic effects of accumulating metabolites on the CNS

Lethargy, poor feeding, sepsis-like(no risk factors),

Seizures, abnormal muscle tone, cerebral edema, ICH

apnea,tachypnea, recurrent vomiting,

Basic laboratory studies

CBC, DC
Urinalysis
Blood gases
Serum electrolytes
Blood glucose, lactate, CSF lactate
Plasma ammonia
Urine reducing substances
Urine ketones if acidosis or hypoglycemia
+
Plasma and urine amino acids
Urine organic acids
Plasma lactate
Urine metabolic screening
Tandem mass (血片)

Hyperammonemia

Unexplained vomiting, lethargy, or other evidence of an encephalopahty

Urea cycle defects, organic acidemias, transient hyperammonemia of the newborn, fatty acid oxidation defects

Frequently > 1000μmol/L (v.s. < 500μmol/L in sepsis, herpes simplex infection, perinatal asphyxia)

Metabolic acidosis

Organic acidemias:Neutropenia, thrombocytopenia, elevated plasma lactate, hyperammonemia

Defects in pyruvate metabolism, or in the respiratory chain

Lactic acidosis , normal urine organic acid

Plasma lactate/pyruvate ratio,

< 25 defect in pyruvate dehydrogenase or in gluconeogenesis

> 25 pyruvate carboxylase defeiciency, respiratory chain defect, mitochondrial myopathy

Metabolic disease without metabolic acidosis or hyperammonemia

nonketotic hyperglycinemia

molybdenum co-factor deficiency

Major inborn errors of metabolism presenting in the neonate as an acute encephalopathy

Disorders	Metabolic acidosis	Hyperam m-onemia	Others
Organic academia	+	+	↑plasma and urine ketones abnormal urine organic acids
Urea cycle defects	−	+ +	Abnormal plasma amino acids
Maple syrup urine disease	+	−	↑plasma and urine ketones ferric chloride test + abnormal plasma amino acids
Nonketotic hyperglycinemia	−	−	Abnormal plasma amino acids
molybdenum co-factor deficiency	−	−	Low serum uric acid ↑sulfites in urine

Emergency treatment of the infant with an acute metabolic encephalopathy

1. Removal of accumulating metabolites

- Suspicion of a disorder associated with protein intolerance → DC protein intake
- Hyperammonemia → hemodialysis
- Urea cycle defect → 0.6mL/Kg 10% arginine HCL IVD 90 minutes
- Organic academia → Cofactor

Cofactors(mg/d)	Disorders
Thiamin, B1(10-50)	MSUD Hyperlactatemia (pyruvate dehydrogenase)
Biotin (10-20 p.o.)	Propinoic aciduria Multiple carboxylase deficiency Hyperlactatemia (pyruvate carboxylase)
Cobalamin, B12(1-2 i.m.)	Methylmalonic aciduria
Riboflavin, B2(20-40)	Glutaric aciduria ß-Oxidation defects
Carnitine (50-100 p.o, 400 i.v.)	Branched-chain organic acidemia` Dicarboxylic acidemia Primary hyperammonemia Hyperlactatemia

- IV bicarbonate

Exchange transfusion

MSUD, methylmalonic, propinoic, and isovaleric acidurias, urea cycle defect.

Transient effect

Applied in association with other methods such as peritoneal dialysis.

Multiple exchanges: 1.5- 4-volume exchanges 4-6 times/d

Continuous exchange: 600ml/k within 15 hours

Fresh blood, slow cycle

Peritoneal dialysis

Warmed dialysate solutions buffered with bicarbonate, 40-50 ml/kg

One hour cycle (15 min filling up, 30 min dwell time, 15 min drainage) over 24-36 h

Methylmalonate has a spontaneous renal clearance twice higher than that of PD

Hemodialysis

Two – 4 hour hemodialysis cycles in MSUD and PA.

Most effective and rapid method or removing small solutes

2. Prevention of catabolism

IV glucose, lipid(如果食物中的指防與疾病無關時),

Complete protein restriction 2-3 d → 0.5g protein/kg/24hours then 1.0g/k/24h

Hypoglycemia

Disorders of carbohydrate metabolism

Glycogen storage diseases :hypoglycemia, hepatomegaly, lactic acidosis

GSD type II pompe disease:macroglossia, hypotonia, cardiomegaly, hepatomegaly, no hypoglycemia

Galactosemia, hereditary fructose intolerance

Defect in fatty acid oxidation

Nonketotic hypoglycemia, hyperammonemia, metabolic acidosis, elevated transaminases, hepatomegaly (Reye like syndrome), sudden death,(medium-chain acyl CoA dehydrogenase deficiency), cardiomyopathy, arrhythmias, unexplained cardiac arrest (very long-chain fatty acyl CoA dehydrogenase deficiency)

Dx:urine organic acid analysis, serum carnitine, plasma acylcarnitine profile

Rx:avoidance of fasting, provision of adequate glucose, restriction of dietary fat intake, supplemental L-carnitine therapy

Jaundice and liver dysfunction

Disorder	Laboratory studies
Galactosemia	Urine reducing substances, RBC galactose-1-phosphate uridyl transferase
Hereditary tyrosinemia	Plasma amino acid, urine succinylacetone
α1-antitrypsin deficiency	Quantitative serum α1-antitrypsin, protease inhibitor typing
Neonatal hemochromatosis	Serum ferritin, liver biopsy
Zellweger syndrome	Plasma very long-chain fatty acids
Niemann-Pick disease type C	Skin biopsy for fibroblast culture, studies of cholesterol esterification and accumulation
GSD type IV	Liver biopsy for histology and biochemical analysis, skin biopsy with assay of branching enzyme in cultured fibroblasts

Galactosemia

Jaundice, liver dysfunction, vomiting, diarrhea, poor weight gain, cataract formation, hypoglycemia,

Finding suggestive of a storage disease

Hepatosplenomegaly in the first few months

GM1-gangliosidosis type I, Gaucher disease, Niemann-Pick disease, Wolman diseaseGSD

Coarse facial features, hepatosplenomegaly, skeletal abnormalities, hernia:GM1-gangliosidosis, mucolipidosis, (I-cell disease), Mucopolysaccharidosis type VII (β Glucuronidase deficiency), sialidosis→ urine screening test for mucopolysaccharides and oligosaccharides

Abnormal odor

Disorder	Odor
Glutaric acidemia typeII	Sweaty feet
Hawkinsinuria	Swimming pool
Isovaleric acidemia	Sweaty feet
MSUD	Maple syrup
Methionine malabsorption	Cabbage
Multiple carboxylase deficiency	Tomcat urine
Oasthouse urine disease	Hops-like
PKU	Mousy or musty
Trimehylaminuria	Rotting fish
Tyrosinemia	Rancid,fishy, or cabbage-like

Dysmophic features

Disorders associated with multiple defects in peroxisomal enzymes

Zellweger syndrome, neonatal adrenoleukodystrophy

Congenital hypotonia, dysmorphic features (epicanthal folds, Brushfield spots, large fontanel, simian creases, renal cyst)

Glutaric academia type II

High forehead, hypertelorism, low set ears, abdominal wall defects, enlarged kidneys, hypospadias, rocker bottom feet

Smith-Lemli-Opitz syndromes

Dysmorphic facies, cleft palate, congenital heart disease, hypospadias, polydactyly, snydactyly, inborn error of cholesterol biosynthesis

Agenesis of the corpus callosum: nonketotic hyperglycinemia, PDH deficiency,
Cataracts:galactosemia, Zellweger syndrome, Lowe syndrome,
Dislocated lenses:homocystinuria, molybdenum co-factor deficiency, sulfite oxidase deficiency
Retinal degenerative change: peroxisomal disorders,

Samples to obtain from a dying child with a suspected inborn error of metabolism

Urine, frozen
Plasma, separated from whole blood and frozen
Blood in ETDA tube (for DNA), 血片，填滿四個洞
Small snip of skin obtained using sterile technique and stored at room temperature or 37 C in tissue culture medium or sterile saline
Unfixed liver tissue frozen at –20C

Reference:

Burton BK. Inborn errors of metabolism in infancy: A guide to diagnosis Pediatrics 102(6) http://www.pediatrics.org/cgi/content/full/102/6/e69