

Disorders of Amino Acids, Organic Acids and Fatty Acids

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Introduction

With the recent advances in laboratory investigations and molecular genetics, the number of known hereditary diseases has increased tremendously in the past decade. Currently, there are nearly 14,000 entries in *Mendelian Inheritance in Man*, of which about 10,000 have established gene loci. Eighty percent of them are inherited in an autosomal recessive manner.

Inborn errors of metabolism (IEM) are a group of genetic disorders with enzymatic, membranous or receptor defects. These result in accumulation of intermediate by products, lack of essential metabolites, or deficiency in energy supply. The molecular property of the substrate determines the dimension of the pathological lesion. The diagnosis is often difficult, as the clinical manifestations are nonspecific in most cases. However, some of them are treatable if diagnosed early. Laboratory diagnosis frequently relies on the identification of quantitative/qualitative alternation of particular substances. The major types of IEM include amino acidopathy, organic academia or aciduria, fatty acid oxidation defects, peroxisomal disorders, glycometabolic disorders, nucleic acid metabolic disorders, and lysosomal disorders.

Clinical Features

The family history may reveal parental consanguinity, siblings with unexplained diseases ("encephalopathy",

"sepsis", SIDS), familial disorders (such as progressive neurological disease, maternal phenylketonuria, multiple miscarriages), or malnutrition. In the neonatal period, IEM may present as neurological symptoms such as feeding problems, abnormal breathing, hypotonia, lethargy, coma, or seizures. The other manifestations include vomiting, diarrhoea, jaundice, growth retardation, hepatomegaly, hypoglycaemia, liver failure, cardiomyopathy, arrhythmia, hyperammonaemia, and metabolic acidosis. One third of the cases may have asymptomatic intervals or of late-onset, with the disease triggered by fever, infection, or protein intake. The clinical course is characterised by periodic metabolic acidosis, ataxia or come; preceded by vomiting, lethargy, hypotonia, or seizure. These may ultimately result in severe CNS injury or death. Specific triggers of metabolic decompensation are summarised in Table 1.

Some of the IEM may present with chronic progressive symptoms, including anorexia, feeding problems, vomiting, diarrhoea, progressive developmental retardation, seizures, ataxia, language delay, autism, mental retardation, hypotonia, or progressive myopathy. The other manifestations include congenital brain malformation, spinal cord symptom, peripheral neuropathy, failure to thrive, chronic liver/kidney/heart diseases, and immunodeficiency. The presentations of specific groups of disorders are summarised as follows:

Disorders in Amino Acid Metabolism

In general, the brain, liver and kidneys are the organs most frequently affected in this group of disorders. The clinical manifestations depend on the specific toxicity of the accumulating metabolites, concurrent product deficiency, severity of the enzyme deficiency, extent of protein intake, and endogenous amino acid release in catabolism. They may present in the neonatal period, late infancy, or puberty. The clinical features are diversified, including acute coma/ataxia/encephalopathy, acute

Table 1 Specific triggers of metabolic decompensation (Zschocke/Hoffmann)

Triggers	Groups of disorders
Fasting, infections, fever, vaccination, operations, accidents	Disorders of protein, energy, and carbohydrate metabolism
High protein intake and/or protein catabolism	Protein metabolism: aminoacidaemias, organic acidurias, urea cycle defects
Major alterations in carbohydrate intake	Mitochondriopathies
Rapidly absorbed carbohydrates	Hyperinsulinism, mitochondriopathies
Fruit, table sugar (sucrose)	Fructose intolerance
Lactose, milk protein	Galactosaemia
High fat intake	FAOD, lipoprotein lipase deficiency, glycerol kinase deficiency
Drugs	Porphyrias, G6PD, FAOD

deterioration or prolonged disease course of a non-specific infection, progressive symptoms, multi-system disorders, metabolic acidosis, ketonuria, and hypoglycaemia. In a suspected case of amino acid disorder, we should collect blood and urine sample for blood count, electrolytes, sugar, liver and renal functions, ammonia, lactate, plasma amino acids, and urine organic acids before therapy.

Organic Aciduria

The clinical presentations are variable. In the neonatal period, the features are that of "intoxication type" metabolic encephalopathy. Some patients have a chronic intermittent presentation characterised by recurrent episodes of ketoacidotic coma, lethargy, ataxia, focal neurological signs, and Reye syndrome. The chronic progressive form may present as failure to thrive, chronic vomiting, anorexia, osteoporosis, hypotonia, developmental retardation, and recurrent infections. Secondary organic aciduria may result from certain drugs and food intake, bacteria in the gut, prematurity, renal failure, and asphyxia.

Disorders of Fatty Acid Oxidation

This group of disorders include carnitine transporter deficiency, carnitine palmitoyltransferase I deficiency, carnitine translocase deficiency, carnitine palmitoyltransferase II deficiency, short-chain acyl-CoA dehydrogenase (SCAD), medium-chain acyl-CoA dehydrogenase (MCAD), long-chain acyl-CoA dehydrogenase (LCAD), long-chain hydroxyacyl-CoA dehydrogenase (LCHAD), and multiple acyl-CoA dehydrogenase (glutaric aciduria II). They typically present in late infancy or early childhood as hypoketotic hypoglycaemic coma during catabolic states (e.g. prolonged fasting, operations or infections). The other features include signs of liver failure with hyperammonaemia, myopathy and cardiomyopathy. The pathogenesis is related to insufficient energy production during fasting, deficiency of mitochondrial free CoA, and accumulation of toxic long-chain acylcarnitines. A useful screening test is the detection of dicarboxylic aciduria during decompensation.

Sudden Infant Death Syndrome (SIDS/SUDS)

It is not uncommon for infants with IEM to present as SIDS. In a review involving 7058 cases of SIDS, 66 were found to have IEM, including 55 cases of fatty acid oxidation disorders and 11 cases of organic aciduria.¹

Laboratory Investigations

The initial investigations should include assessment for

abnormal urine colour/odor, and screening tests such as reducing substance. We should check the complete blood count, blood gases, acid base status, electrolytes, glucose, liver function, ketones, ammonia, lactate, and pyruvate. Qualitative urine amino acid analysis may be performed by thin layer chromatography (TLC) and high voltage electrophoresis (HVE/TLC). Quantitative amino acid analysis may be performed by amino acid analyzer, high performance liquid chromatography (HPLC), and tandem MS. Organic acid and acylcarnitine analysis may be done by gas chromatography, gas chromatography/mass spectrometry (GC/MS), and tandem MS. GC/MS was first utilised by Tanaka in 1966 for the diagnosis of isovaleric academia. Since then, over 70 different types of organic academia has been identified. Many of these disorders are treatable if diagnosed early. The investigation protocols for neonatal hyperammonaemia and metabolic acidosis with increased anion gap are summarised in Figures 1 and 2.²

Principles of Treatment for IEM

- a) Decrease the production of toxic substance by diet restriction, energy substitution, NTBC, and antibiotics.
- b) Clearance of intermediate metabolites by diuretics, dialysis, haemofiltration, and medications such as sodium benzoate.
- c) Replacement of essential products, such arginine; or via gene transfer.
- d) Appropriate symptomatic management, such as fluid and electrolyte replacement and correction of acidosis.

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References

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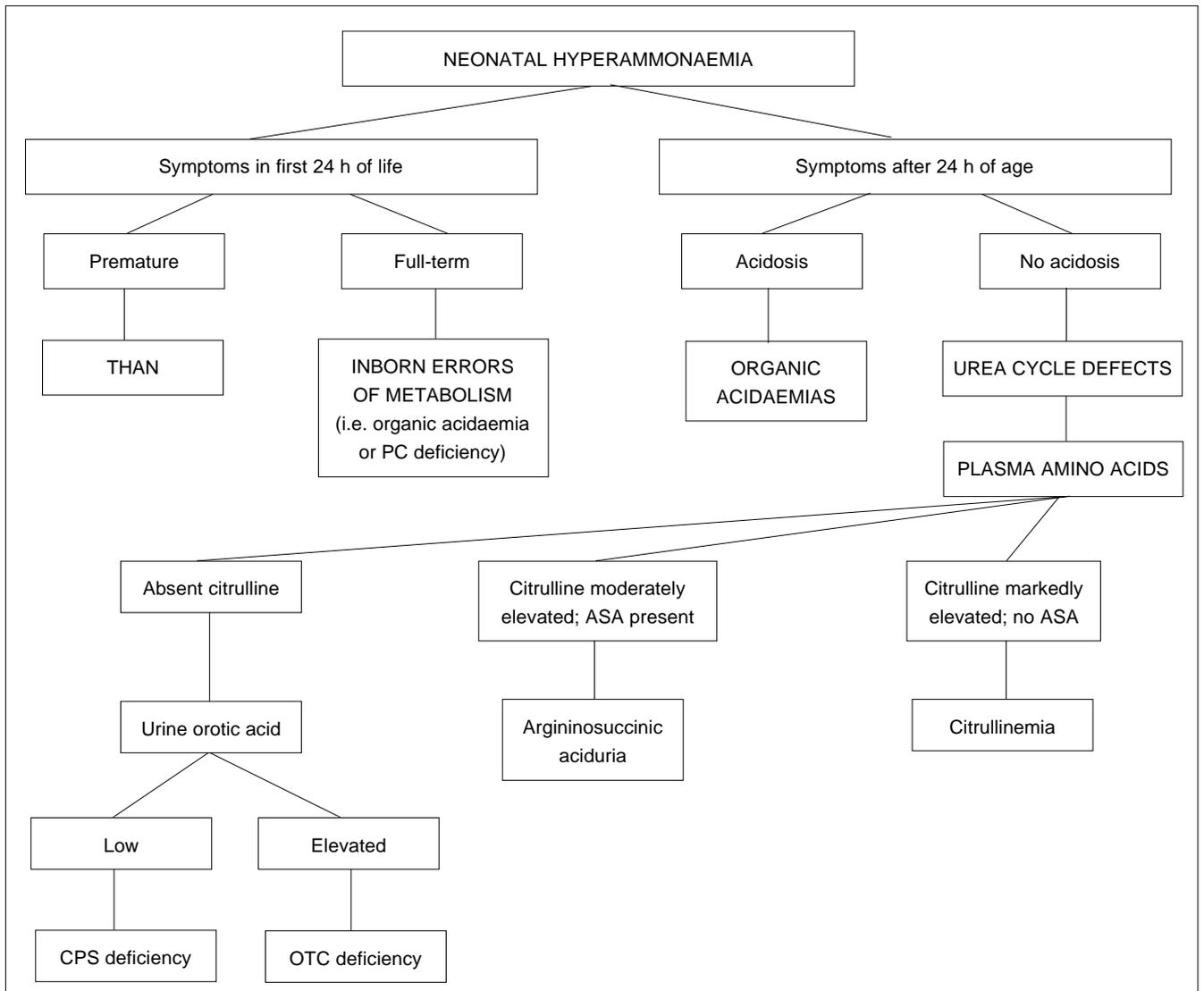


Figure 1 Differentiation of conditions associated with neonatal hyperammonaemia.

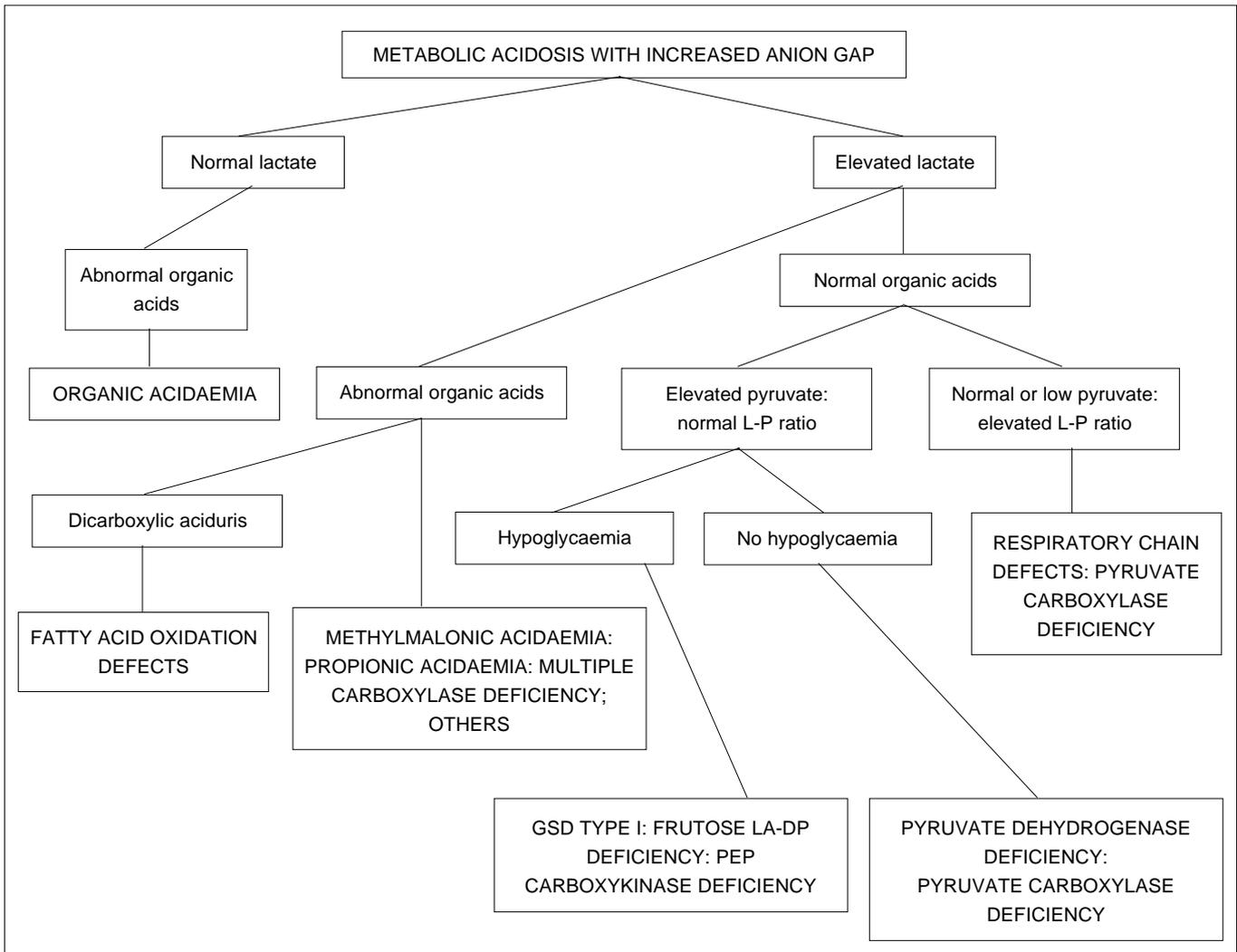


Figure 2 Evaluation of metabolic acidosis in the young infant.