CLINICAL EVALUATION AND EMERGENCY MANAGEMENT OF INBORN ERRORS OF METABOLISM PRESENTING IN THE NEWBORN

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Abstract. Close to 500 biochemically diverse genetic metabolic disorders have been identified. Despite their diversity, these diseases share a number of features. First, the majority of patients with an inborn error present clinically with one of five general phenotypes; acute encephalopathy, progressive encephalopathy, primary muscle disease, primary liver disease or primary renal disease. Encephalopathy is by far the most common clinical manifestation of inborn errors of metabolism, and may be acute, intermittent, chronic (progressive), or even non-progressive. Although the five major phenotypes are a useful clinical guide, other clinical presentations of course occur, and some are virtually specific to a single disease or group of disorders. Second, almost all inborn errors are recessive in inheritance, and most of these conditions map to one of the 22 autosomes. Third, specific and effective treatment of inborn errors is often made possible by our understanding of their biochemical bases. Because inborn errors are genetic diseases, families with affected children can be made aware of the risk of recurrence, through genetic counselling. In many instances, presymptomatic treatment of affected relatives, carrier testing, and prenatal diagnosis can be offered. The types of inborn errors and their mode of presentation in the newborn are discussed, along with a schema permitting their rapid diagnosis. The principles of emergency and long term management are also discussed, with particular emphasis on those disorders that present in the newborn period with an acute encephalopathy, the so-called "small molecule" disorders.

INTRODUCTION

Genetic metabolic disorders are inherited diseases that interfere with normal metabolic function. When one of these conditions is detected clinically and by screening tests, specific biochemical investigations to establish the exact nature of the abnormality must be performed urgently if appropriate therapy is to be instituted early enough to prevent death or permanent damage. This paper focuses on disorders that present as an acute encephalopathy, particularly in the newborn period.

Over 500 biochemically distinct inborn errors have been identified, but despite their diversity, most of these disorders manifest themselves in one of five clinical presentations (Table 1). Almost all inborn errors are autosomal recessive in inheritance. Certain genetic clues should alert one to the possibility of a genetic metabolic disorder: 1) history of a similarly affected sib or other affected relative; 2) parental consanguinity; 3) ethnicity (some disorders are more common in certain ethnic groups); 4) parents come from the same small town or village and 5) parental isonomy (same last name)

For most of these disorders the clinical and biochemical consequences are due to either an accumulation of toxic metabolites, or a deficiency of essential products. It is important to remember that, with accumulation of toxic metabolites; 1) most small molecule diseases affect enzymes in catabolic pathways; 2) catabolic processes such as infections will overload already compromised enzyme function; 3) noxious molecules which accumulate include amino acids, organic acids, fatty acids and their esters, and ammonium ; 4) hepatomegaly and signs of generalized hepatic dysfunction are often found. Brain involvement in the disease process reflects its vulnerability to metabolic disturbance, rather than greater enzymatic activity within. Product deficiency, meanwhile, includes disorders that impair energy production, resulting in intracellular depletion of ATP, such as defects of gluconeogenesis, defects of pyruvate metabolism, Krebs cycle defects and mitochondrial respiratory chain defects.

Table 1. The common clinical presentations of inborn errors of metabolism (from Rudolph's fundamentals of pediatrics. 3rd ed. McGraw Hill, 2002: 222, reproduced with permission of the McGraw-Hill Companies).

Clinical presentation	Disease (with examples)
Encephalopathy	*Acute encephalopathy* Diseases of small diffusible molecules • amino acid disorders (maple syrup urine disease) • organic acid disorders (methylmalonic aciduria) • fatty acid oxidation defects (medium chain acyl-CoA dehydrogenase [MCAD] deficiency) • hyperammonemias (ornithine transcarbamylase deficiency) • lactate and mitochondrial disorders (cytochrome oxidase deficiency) • encephalopathy with seizures (nonketotic hyperglycinemia) *Chronic encephalopathy* Diseases of small diffusible molecules Diseases of organelles *Mitochondrial disorders* - defects in pyruvate and electron transport bioenergetics • electron transport chain defects (cytochrome c oxidase deficiency) • defects of pyruvate metabolism (pyruvate dehydrogenase deficiency) *Lysosomal storage disorders* • mucopolysaccharidoses (Hurler disease) • glycoproteinoses (α-mannosidosis) • gangliosidoses (GM2 gangliosidosis) • other sphingolipidoses (Gaucher disease) • leukodystrophies (metachromatic leukodystrophy) *Peroxisomal disorders* • defects of peroxisomal biogenesis & β-oxidation (Zellweger syndrome) • Rhizomelic chondrodysplasia punctata • X-linked adrenoleukodystrophy • other defects of single peroxisomal enzymes (oxalosis) Disorders of protein glycosylation – includes enzyme defects localised to: *Cytosol* • carbohydrate-deficient glycoprotein syndrome types Ia and Ib *Golgi body disorders* • carbohydrate-deficient glycoprotein syndrome type II *Endoplasmic reticulum* • carbohydrate-deficient glycoprotein syndrome types Ic and V
Diffuse hepatocellular disease	*Acute or chronic liver disease* • defects of carbohydrate metabolism (galactosemia) • defects of amino acid metabolism (tyrosinemia) • defects of metal transport (Wilson disease) • defects of protease inhibitors (α1-antitrypsin deficiency)
Myopathy	*Skeletal myopathy* • acute rhabdomyolysis (muscle phosphorylase deficiency) • chronic myopathy (mitochondrial electron transport chain defects; fatty acid metabolism defects) *Cardiomyopathy* • lysosomal storage disorders (Pompe disease: α-glucosidase deficiency) • disorders of fatty acid metabolism (long-chain 3-hydroxyacyl-CoA dehydrogenase [LCHAD] deficiency)
Renal tubular disease	*Glomerular and tubular disease* • lysosomal storage disorder (cystinosis) • enzyme defect (oxalosis) *Transport defects* • defective transport of individual or groups of similar molecules (cystinuria)
Disorders with distinctive phenotypes	*Hepatomegaly without dementia* • defects of gluconeogenesis (glucose-6-phosphatase deficiency) • lysosomal storage disorders (Gaucher disease - nonneuronopathic variant) • "Cerebral palsy" without a history of perinatal distress • five different enzymopathies (Lesch-Nyhan syndrome) [HPRT deficiency] *Stroke or thrombosis* • increased risk of thrombosis (homocystinuria) • other diverse conditions (MELAS syndrome) *Disorders causing facial dysmorphism or congenital malformations* • due to teratogenic metabolites (maternal phenylketonuria) • impairment of cellular bioenergetics (pyruvate dehydrogenase deficiency) *Premature atherosclerosis* • defects of lipoprotein metabolism (familial hypercholesterolemia) *Menkes disease* • a disorder of copper metabolism with a unique phenotype

Because the newborn period is a time of substantial catabolism, the breakdown of protein and fat results in increased delivery of metabolites to the pathway blocked by the genetic defect, and consequent elevations of the metabolite levels. Infants who have slightly more residual enzyme activity, with a less severe metabolic block, may escape presentation in the newborn period only to develop symptoms later in infancy, or even later in life, when they are exposed to more substrate such as increased protein or fat intake (for example by a switch from breast milk to a cow's milk based formula), or breakdown of body protein or fat due to infection, starvation, or trauma (including surgery). Many of the encephalopathic metabolic crises that intermittently affect well-treated patients are also precipitated by catabolic stress. The recognition of subtle signs of impending metabolic decompensation, such as the development of ataxia or changes in behaviour, permits the early institution of emergency therapy to prevent progression of the episode to acute encephalopathy.

CLINICAL PRESENTATIONS

Acute encephalopathy

Encephalopathy is the most common clinical presentation of genetic metabolic disorders. It can be acute, intermittent, chronic, or even non-progressive. Patients with a **severe** enzyme defect often present in the newborn period or early infancy, but small molecule diseases may cause acute encephalopathy at any age, and must be excluded even in adults with unexplained acute encephalopathy. This category of inborn errors includes: 1) Amino acidopathies (eg maple syrup urine disease); 2) Organic acidopathies (eg methylmalonic acidemia); 3) Fatty acid oxidation defects (eg medium chain acyl-CoA dehydrogenase deficiency); 4) Urea cycle defects (eg ornithine transcarbamylase deficiency); 5) Primary lactic acidosis disorders (including defects of gluconeogenesis, the Krebs' cycle, pyruvate metabolism and the mitochondrial respiratory chain)

Amino acidopathies. Amino acids are essential for endogenous protein synthesis, but once anabolic needs are met, the surplus is degraded and used for energy. In the amino acidopathies these degradative pathways are disrupted. Catabolism and excess amino acid intake leads to accumulation of the toxic metabolite. A classic example is maple syrup urine disease, a catabolic defect of the three branched-chain amino acids leucine, isoleucine and valine, caused by a defect of the enzyme branched-chain α-ketoacid dehydrogenase.

Organic acidoses. Organic acidopathies should be considered in any patient with a metabolic acidosis. Accumulation of organic acids, products of the later steps of the breakdown of the carbon chain of the amino acids, causes a more severe metabolic acidosis than that seen in the aminoacidopathies, with a compensatory hyperpnea. The catabolic pathways of the various amino acids result in the formation of many different organic acid intermediates, which for a particular disorder results in a characteristic biochemical signature, detectable by gas chromatography/mass spectrometry of urine or plasma. The most common of these is methylmalonic aciduria, most often due to mutations in the enzyme L-methylmalonyl-CoA mutase. Functional abnormalities in this enzyme lead to an inability to catabolise isoleucine, valine, threonine and methionine, odd chain fatty acids, and the side chain of cholesterol.

A clue to the presence of an organic acid accumulation is an increase in the anion gap. Organic acidopathies must be excluded if the anion gap is greater than 20 mEq/l. Most patients with an increased anion gap do not have an inborn error of metabolism, but an acquired acidosis either from lactic acidemia secondary to tissue hypoxia, or from ketone body accumulation (ketoacidosis), for example in diabetes mellitus. A normal anion gap does not exclude significant lactic acidemia, as it may remain normal until the blood lactate exceeds 6 mmol/l.

Fatty acid oxidation defects. Following prolonged fasting in normal children, hepatic glycogen stores become depleted, causing the brain and muscle to use fatty acids liberated by lipolysis as the major energy source. These fatty acids undergo β-oxidation, generating ketone bodies, which can be directly utilised by muscle and brain. The decrease in ketone body production in children with fatty acid β-oxidation defects results in hypoketotic hypoglycemia. These disorders are therefore usually exposed by fasting. Consequently, an inherited disorder of fatty acid β-oxidation should be suspected in any child with fasting coma, lethargy and vomiting, particularly if associated with hepatomegaly, fasting hypoglycemia, skeletal- or cardiomyopathy, acute life threatening episodes, and a family history of sudden infant death syndrome (SIDS). The most common of these is medium chain acyl-CoA dehydrogenase (MCAD) deficiency. As there are a number of other metabolic causes of hypoglycemia, a diagnostic algorithm (Fig 1) can be helpful in arriving at a diagnosis. It cannot be stressed how important it is to collect all the appropriate samples during the hypoglycemic episode to maximize the chance of making the diagnosis rapidly and efficiently.

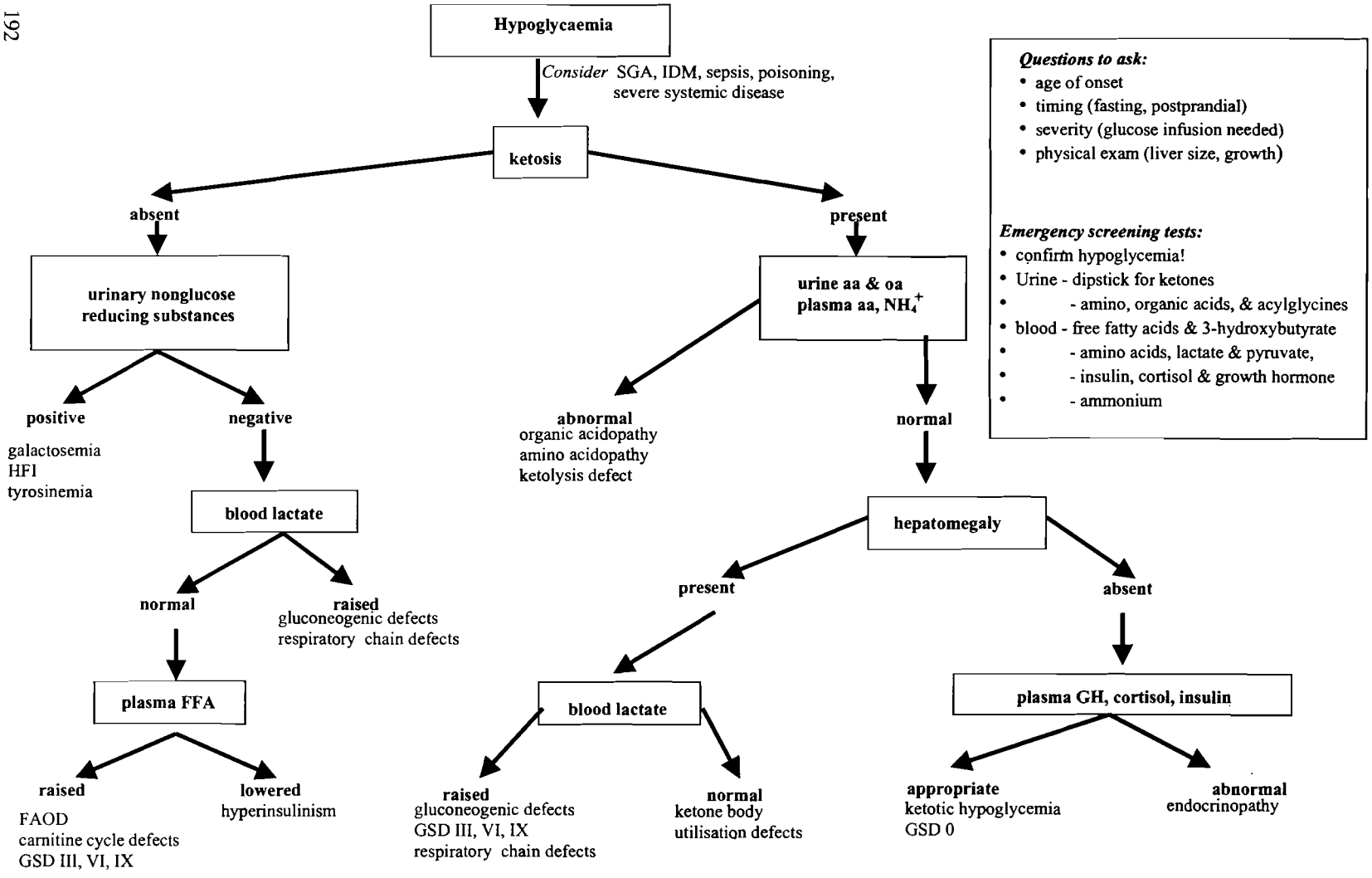

Figure 1: Diagnostic algorithm, for patients presenting with hypoglycemia.
SGA, small for gestational age; IDM, infant of a diabetic mother; HFI, hereditary fructose intolerance, aa, amino acids; oa, organic acids, NH_4^+, ammonium; FFA, free fatty acids; GH, growth hormone; FAOD, fatty acid β-oxidation defect; GSD, glycogen storage disease.

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Acute encephalopathy in the newborn

For newborns presenting with signs and symptoms of acute encephalopathy, the following points should be remembered:

- it takes time for the offending metabolite to accumulate to toxic levels
- the infant is usually well for several days to a week after birth
- symptoms are usually nonspecific and include poor feeding, vomiting, lethargy, hypotonia, irritability, tachypnea and hyperpnea (if metabolic acidosis is also present), seizures (usually a late feature, and an indicator of a poor prognosis)
- cerebral edema occurs frequently with signs of raised intracranial pressure (progressive obtundation, bulging fontanelle)
- failure to thrive is almost always present
- hepatomegaly is often present

The most common alternative diagnoses in an infant with acute encephalopathy are sepsis, perinatal hypoxia, congenital malformation of the heart or gut, or intracerebral hemorrhage. The possibility of an inborn error is often considered only after these have been ruled out, but unless screening investigations for inborn errors are performed in parallel with testing for these more common diseases and appropriate aggressive treatment given, severe neurological damage or death may ensue. Screening tests which should be performed on any newborn or infant with acute encephalopathy are summarised in Fig 2.

Acute encephalopathy beyond the newborn period

A child or adult with a small molecule disease may have good health for years or decades, and then unexpectedly present with an acute encephalopathy. In these patients there is sufficient residual enzyme activity to catabolise the substrate when they are in good health, but the added stress of a catabolic episode results in excessive substrate accumulation. In the *intermittent variant of maple syrup urine disease*, for example, the child is biochemically normal except when challenged by the catabolism of intercurrent illness or excessive protein intake, when ataxia and decreased conciousness, due to accumulation of the branched-chain α-ketoacids, develops.

Occasionally a patient with a disease of this type may not present until adult life. The initial presentation of *ornithine transcarbamylase deficiency* in female carriers may be during the catabolic phase after childbirth. Older patients with small molecule diseases may present with loss of consciousness, ataxia, disorientation or frank psychosis.

The intermittent or late-onset forms of the small molecule inborn errors are commonly misdiagnosed as *Reye syndrome* because of the presence of encephalopathy, cerebral edema, mild liver dysfunction (increases in AST with fatty infiltration of the liver, hypoglycemia and hyperammonemia). Thus, the diagnosis of Reye syndrome should only be made after the exclusion of small molecule inborn errors.

Hyperammonemia

Because ammonium is a potent neurotoxin, hyperammonemia needs urgent investigation for a possible inborn error of metabolism. Hyperammonemia, sometimes severe, is often seen in the organic acidopathies and fatty acid oxidation defects, reflecting a secondary inhibition of the urea cycle by the accumulating metabolites of those disorders. Primary hyperammonemia caused by urea cycle defects usually present in the first week of life, with the most common of these being the X-linked disorder, ornithine transcarbomylase (OTC) deficiency. Neurological impairment is seen in almost all survivors who were diagnosed late, and these infants are at risk of further encephalopathic episodes following excessive protein intake or during catabolic periods. Fig 3 provides an algorithm to aid in the rapid diagnosis of specific metabolic disorders causing hyperammonemia.

Primary lactic acidosis

In a child with lactic acidosis, if poor tissue perfusion due to cardiac disease, hypovolemia, severe sepsis or some other cause of shock have been excluded, the possibility of an inherited defect of pyruvate metabolism, the citric acid (Krebs) cycle, gluconeogenesis, or of the mitochondrial respiratory chain should be suspected. Organs that are heavily energy-dependent, particularly the brain, heart, kidney, skeletal muscle and retina are most often affected, causing a wide range of clinical signs.

These disorders are usually associated with raised blood and/or CSF lactate, and may result in a metabolic acidosis with an increased anion gap, although in some cases the acidosis may be mild and the anion gap normal. In Krebs cycle disorders, urine organic acid analysis can help identify the accumulating organic acid, but for these and the other primary lactic acidoses, enzymatic assay of biopsied liver and muscle is required to confirm the specific enzyme defect. Structural abnormalities of the mitochondria are commonly found in the respiratory chain disorders including "ragged red fibres", which

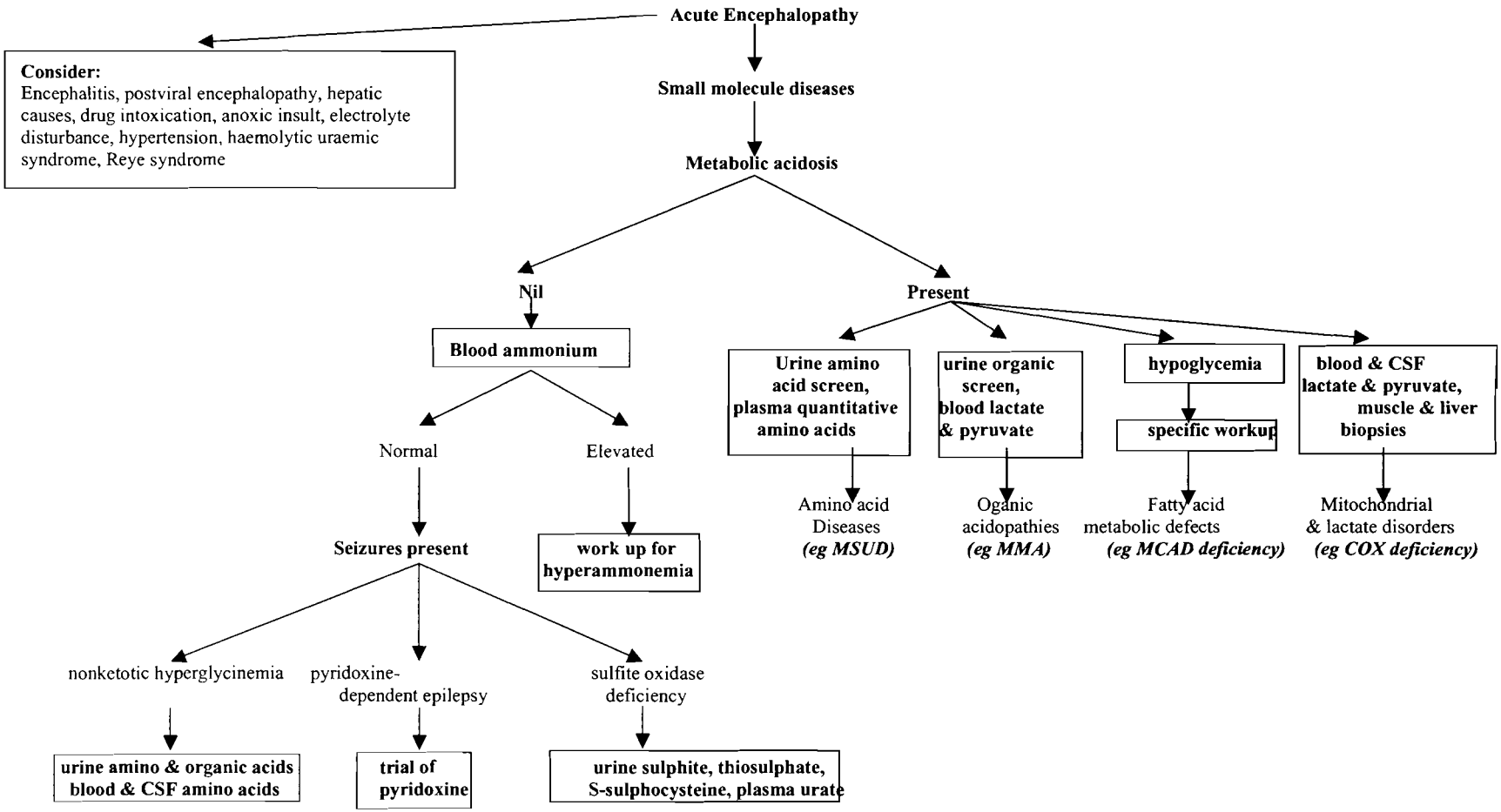

Figure 2: Biochemical Evaluation of Inborn Errors Causing Acute Encephalopathy The five types of small molecules associated with metabolic defects that cause inborn errors are shown, together with the laboratory studies that are required to identify the diseases of each type. As the clinical presentation of these disorders is often similar, a series of screening investigations (highlighted in the boxes) should be performed in all such children. CSF, cerebrospinal fluid

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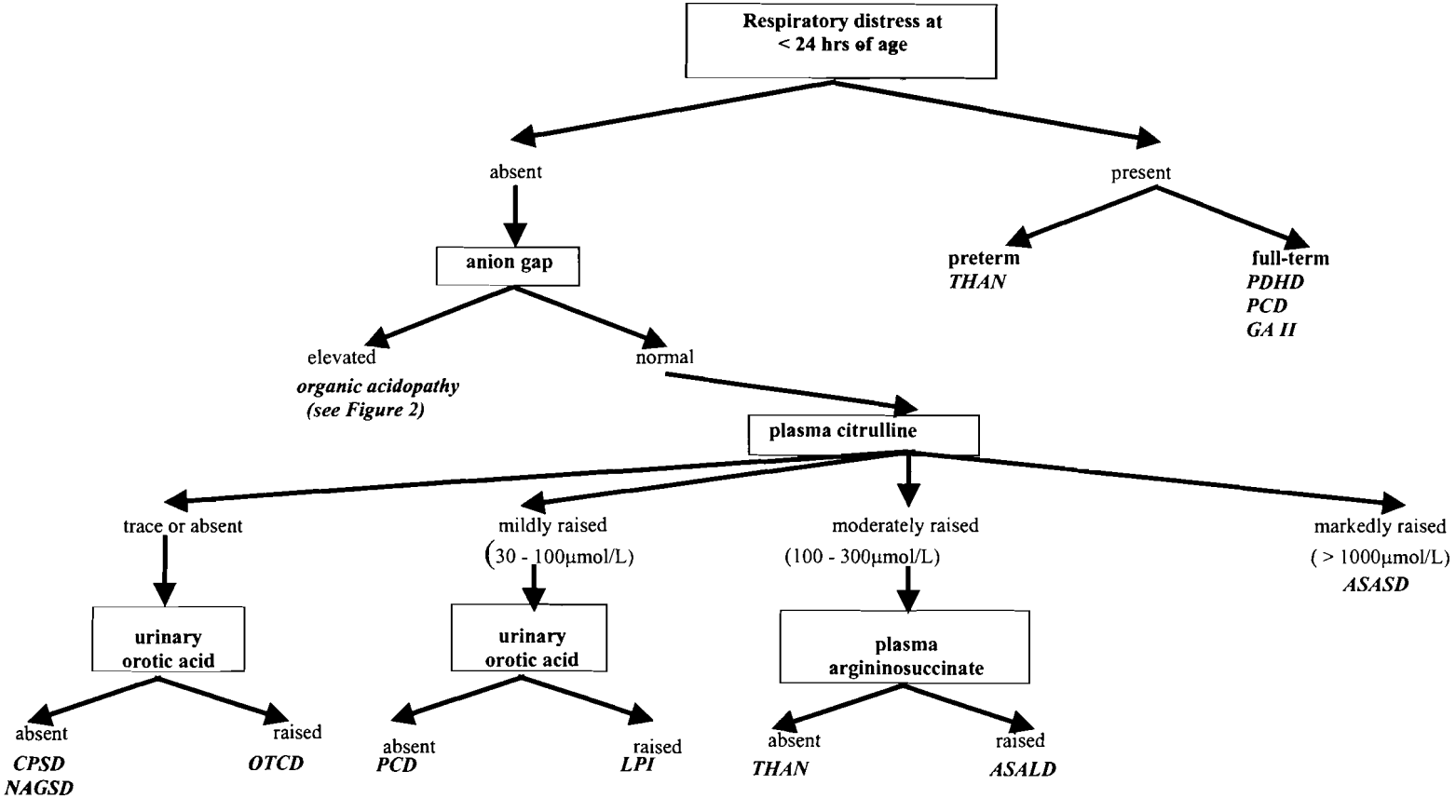

Figure 3: Diagnostic Algorithm for the Hyperammonemic Disorders.
The hyperammonemic disorders can be biochemically distinguished by measuring the anion gap, plasma amino acids (including citrulline and argininosuccinate), and urinary orotic acid. THAN, transient hyperammonemia of the newborn; PDHD, pyruvate dehydrogenase deficiency; PCD, pyruvate carboxylase deficiency; GA II, glutaric aciduria type II; ASASD, argininosuccinic acid synthase deficiency (citrullinemia); CPSD, carbamylphosphate synthase deficiency; NAGSD, N-acetylglutamate synthase deficiency; OTCD, ornithine transcarbamoylase deficiency; LPI, lysinuric protein intolerance; ASALD, argininosuccinic acid lyase deficiency (argininosuccinic aciduria).

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contain peripherally-situated clumps of mitochondria that stain red with the modified Gomori trichrome stain used for light microscopy.

The majority of the respiratory chain disorders are autosomal recessive in inheritance. Defects in mitochondrial DNA (mtDNA), in contrast, are either maternally inherited, or sporadic, and screening for the more "common" mtDNA mutations should be part of the diagnostic workup for respiratory chain defects.

Encephalopathy with predominating seizures

In the disorders described earlier, seizures are a late feature but there are four disorders, nonketotic hyperglycinemia, pyridoxine-dependent epilepsy, sulphite oxidase deficiency, and the molybdenum cofactor deficiency, which are notable for early seizures as the predominant feature. The clinical presentation can be suggestive of perinatal asphyxia, but without a supportive history.

Nonketotic hyperglycinemia (NKH), due to defects of the glycine cleavage system, has a rapidly progressive course in the neonate with profound hypotonia, progressive obtundation, seizures, hiccoughs and apnea. Survivors usually have poorly controlled seizures and profound intellectual handicap.

Pyridoxine (vitamin B6)-dependent epilepsy begins in the first weeks of life (or even *in utero*), and should be excluded in any infant or child with an unexplained seizure disorder. Traditional anticonvulsants do not control the seizures. Other children with pyridoxine-dependent epilepsy may have a later onset (as late as 18 months of age), may be initially or partially responsive to other anticonvulsants, or may have seizure-free periods on no medications. The outcome is variable. Some patients have had good seizure control and normal development, but many others have been intellectually impaired, although this may reflect late diagnosis.

Sulphite oxidase deficiency, a defect of cysteine catabolism, or in the biosynthesis of its *molybdenum cofactor*, produce a remarkably similar phenotype, which usually has its onset in the neonatal period. Typical clinical features in the first week or two of life include feeding difficulties, intractable generalized seizures, and truncal hypotonia with peripheral hypertonia. Those who survive beyond the neonatal period develop progressive destructive brain changes with severe calcification, choreoathetoid movements and lens dislocation. Milder variants have also been described, with less severe neurological and somatic abnormalities and a later onset of symptoms.

MANAGEMENT OF INHERITED SMALL MOLECULE DISORDERS

Acute resuscitative therapy

In patients suspected of having an inborn error of metabolism, it is important to implement immediate resuscitative treatment whilst the diagnostic workup is in progress, and should include:

- Provision of fluid, electrolytes, and glucose
- Correction of the metabolic acidosis
- Hemodialysis or hemofiltration
- Specific therapy according to the disease. For example:
  - -- *Nutritional modification*, such as appropriate caloric supplements (eg intralipid and intravenous amino acid supplements free of the offending precusor amino acids in MSUD).
  - -- *Cofactor administration*, which will sometimes improve the function of a genetically defective metabolic pathway (eg vitamin B_{12} in some cases of methylmalonic aciduria, since adenosylcobalamin is a cofactor for L-methylmalonyl-CoA mutase).
  - -- *Use of alternate metabolic pathways*, such as the administration of sodium benzoate in hyperammonemias, to divert a toxic substrate to a benign excretable form.

Long term therapy of small molecule diseases

For many of these disorders, dietary modifications are used to maintain low levels of the toxic metabolite(s). For example, for MSUD patients, small amounts of leucine, isoleucine, and valine are provided to allow normal growth by giving very small amounts of normal protein-containing foods but avoiding giving excess of these amino acids which would be catabolized to form the toxic ketoacids. An artificial formula including the other essential amino acids, vitamins, minerals and other trace nutrients is provided. Regular blood monitoring of amino acids is necessary. Normal or near-normal neurological outcome is possible for the well-managed patient, depending on the degree and duration of the initial encephalopathic episode, the severity of subsequent metabolic crises, and the quality of the long term metabolic control.

CONCLUSIONS

With early and prompt diagnosis, specific and

effective treatment for those inborn errors which present with acute metabolic failure is often possible, with very gratifying short and long term results. Families with affected children can be alerted to the risk of recurrence through genetic counselling. In many instances, presymptomatic treatment of affected relatives, carrier testing, and prenatal diagnosis can be offered.

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