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Inborn errors of metabolism in the newborn: clinical presentation and investigation

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ABSTRACT Inborn errors of metabolism are genetically determined interruptions of one (or several related) metabolic pathway(s). Clinical symptoms are caused by deficiency of the pathway product and/or toxicity resulting from the accumulation of an intermediary compound. Inborn errors of metabolism are mostly recessive disorders, with clinical symptoms rare in heterozygous individuals. The genetic defects involve homozygous (autosomal) or hemizygous (X-linked) mutations in genes encoding proteins with a single enzymatic function. However, interruptions in biochemical pathways may also result from mutations affecting the bioavailability of an enzymatic co-factor or disordered transport of the enzyme across intracellular membranes. In the latter two circumstances it is likely that more than one enzymatic process will be affected.

The five main modes of presentation of IEM in the neonatal period are acute intoxication, energy deficiency, organomegaly, profound central hypotonia, and malformations. The common diagnoses in each of these groups will be presented, with brief descriptions of the currently available options for diagnosis and therapy.

KEYWORDS Energy deficiency, floppy babies, intoxication syndrome, malformations, therapy, visceral disease

LIST OF ABBREVIATIONS Adenosine triphosphate (ATP), argininosuccinic acid synthetase (ASS), central nervous system (CNS), dichloroacetic acid (DCA), electrocardiogram (ECG), electroretinogram (ERG), fatty acid oxidation disorders (FAOD), inborn errors of metabolism (IEM), isovaleric aciduria (IVA), long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD), maple syrup urine disease (MSUD), methylmalonic aciduria (MMA), non-ketotic hyperglycinaemia (NKH), ornithine transcarbamylase (OTC), oxaloacetic acid (OAA), Oxidative phosphorylation (OXPHOS), propionic aciduria (PA), pyruvate carboxylase (PC), pyruvate dehydrogenase (PDH), Smith–Lemli–Opitz syndrome (7-dehydrocholesterol reductase deficiency) (SLOS), trifunctional protein (TFP)

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CLINICAL PRESENTATIONS OF INBORN ERRORS OF METABOLISM IN THE NEONATAL PERIOD

Early diagnosis and successful treatment of neonatal IEM require consideration of the following points:

- Each condition is individually very rare but collectively they are relatively common.
- Inborn errors of metabolism should not be considered diagnoses of last resort.
- The mode of presentation is a useful clue to the IEM diagnosis (see below).
- Family history may be particularly helpful (e.g. parental consanguinity, neonatal death in siblings or maternally-related male relatives).

There is a limited repertoire of clinical responses to illness seen in the newborn. Non-acute presentations of IEM may result from a prenatal diagnosis if the condition is known within the family or from the national neonatal screening program. In this situation the metabolic specialist should be involved from the outset of care. However, acute presentations in neonates with previously unexpected IEM will most often fall into one of the following categories:

- *The intoxicated infant* – appears normal in the perinatal period followed by a period of rapid generalised deterioration, usually after feeding is established.
- *Energy deficiency state* – commonly associated with recurrent hypoglycaemia and/or lactic acidosis, may resemble intoxication.
- *Prominent visceral involvement* – most often involving isolated hepatic or cardiac dysfunction.
- *The congenitally 'floppy baby' (+/- seizures)* – tend to be recognised as abnormal from birth.
- *Multiple malformation syndromes.*

THE INTOXICATED BABY

A characteristic history would be of a full-term infant with a normal birth weight who is well for the first two or three days of life and then refuses feeds, has recurrent vomiting, and becomes hypertonic and/or comatose. Unless specific treatments are instituted, such a clinical picture would usually progress rapidly to death. This is often confused with sepsis. In some of these disorders the abnormal metabolites may be recognised by an unusual odour. A more useful diagnostic approach can be made on the basis of acid–base balance, glucose/lactate homeostasis, and ammonia level. Saudubray *et al.*[1] presented a 20-year survey of IEM presenting in the neonatal period and showed that despite the large number of possible diagnoses, 72·5% of the cases were due to seven disorders in three categories:

- *Aminoacidopathies* (MSUD and NKH) usually diagnosed by plasma amino acid chromatography.
- *Organic acidurias* (MMA, IVA, and PA) diagnosed by urinary organic analysis.
- *Hyperammonaemias* (OTC deficiency and citrullinaemia) usually diagnosed by plasma ammonia estimation and amino acid chromatography.

Aminoacidopathies

Maple syrup urine disease is the most common single IEM presenting in the neonatal period, accounting for ~12% of all cases.[1] Maple syrup urine disease is caused by homozygosity for mutations in the genes encoding the subunits of the branched chain α-keto acid dehydrogenase complex. These mutations (which may affect any of the subunits) result in accumulation of the branched chain amino acids (leucine, isoleucine, and valine). Unusual clinical features include boxing and pedalling movements and the lack of significant acidosis. The diagnosis of MSUD is based on the greatly increased levels of these amino acids (particularly leucine) in the blood, cerebrospinal fluid, and urine.

Non-ketotic hyperglycinaemia accounts for ~10% of IEM presenting in the neonatal period.[1] In non-ketotic hyperglycinaemia, abnormal quantities of glycine accumulate in all body tissues as a result of an inborn error of the glycine cleavage pathway. Mutations have been identified in the components (P, H, T, and L proteins) of a mitochondrial enzyme complex. Seizures are a prominent component of this disorder and are often associated with a characteristic burst-suppression pattern on EEG. The diagnosis is usually established by demonstrating a cerebrospinal fluid:plasma glycine ratio greater than 0·08. Organic acid analysis should be performed to exclude organic aciduaria, e.g. propionic acidaemia (ketotic hyperglycinaemia). Enzymatic confirmation requires the measurement of glycine cleavage activity in the liver.

Organic acidurias

Methylmalonic aciduria is a product of dysfunction of the enzyme methylmalonyl-CoA mutase. This catalyses the conversion of methylmalonyl-CoA to succinyl-CoA and is an adenosylcobalamin (a vitamin B12 derivative) dependent enzyme. Thus mutations in the genes encoding either the mutase enzyme itself, or the enzymes involved in cobalamin synthesis, can produce MMA. The diagnosis is based on the presence of urinary methylmalonate and specific enzyme assays.

Isovaleric aciduria is due to isovaleryl-CoA dehydrogenase deficiency. This enzyme converts isovaleryl-CoA to 3-methylcrotonyl-CoA as an intermediary step in the catabolism of leucine. The diagnosis is made by demonstrating isovalerylglycine in urine. It is this substance that gives these patients the characteristic 'sweaty feet' smell.

Propionic aciduria Propionyl-CoA carboxylase is a biotin-dependent enzyme that catalyses the conversion of propionyl-CoA (a by-product of the catabolism of several amino acids, odd-chain fatty acids, and cholesterol) to methylmalonyl-CoA. Deficiency of this enzyme results in massive accumulation of propionic acid in all tissues and such patients often show a, currently unexplained, ketotic hyperglycinaemia. Diagnosis is made on the finding of urinary propionate and demonstration of enzyme deficiency (possible in many tissues including liver, leucocyte, and fibroblasts).

Hyperammonaemias

In this category the most common IEMs presenting in the neonatal period are defects in the urea cycle which account for ~21% of all IEMs presenting in the neonatal period.[1] This enzymatic cycle is present in the liver and intestine and converts toxic nitrogenous waste into the water-soluble compound urea. A severe deficiency in this cycle results in the typical history of a full-term baby who becomes acutely unwell (lethargic, hypothermic, tachipnoeic, and refusing feeds) on day four with a respiratory alkalosis and very high plasma ammonia. Such a presentation may be rapidly fatal even with full supportive therapy.

Ornithine transcarbamylase deficiency is caused by mutations in the OTC gene located on Xp21. Ornithine transcarbamylase catalyses the formation of citrulline from ornithine and carbamyl phosphate. Thus, deficiency results in hypocitrullinaemia and high levels of urinary orotic acid, a product of carbamyl phosphate metabolism by the pyrimidine synthetic pathway. These biochemical features are very useful in making the diagnosis, which may be confirmed by enzyme assay in the liver.

Citrullinaemia is caused by deficiency of ASS. The ASS gene is located on 9q34. The diagnosis is usually made on

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plasma amino acid analysis by finding plasma citrulline levels of 1,000–5,000 μM (normal 10–20 μM).

Organic acid analysis should always be performed since a number of organic acidaemias may also present with hyperammonaemia, notably propionic and MMA.

ENERGY DEFICIENCY STATES

Congenital hyperlactataemias

Lactic acid is the product of the anaerobic metabolism of glucose via enzymatic reduction of pyruvate (by lactate dehydrogenase) and can only be removed by a reversal of this process. The normal lactate:pyruvate ratio in human plasma is between 10:1 and 25:1. High lactate levels can be caused by many non-genetic diseases, including tissue necrosis and sepsis. This is due to the reduced level of oxygen in tissues that normally rely on the oxidative metabolism of glucose. Hypoxia produces this effect by inhibiting the production of ATP by oxidative phosphorylation, while at the same time stimulating the production of lactate by increasing the rate of glycogenolysis. This produces a much increased lactate:pyruvate ratio. Two groups of IEM commonly present with congenital hyperlactataemia (accounting for ~13% of neonatal IEM).

Disorders of pyruvate metabolism PDH and PC are the most common deficiencies. Pyruvate dehydrogenase is a multienzyme complex made up of four subunits (E1α, E1β, E2, and E3) and catalyses the conversion of pyruvate to acetyl-CoA. Most deficiencies are due to the E1α gene on Xp22. Pyruvate carboxylase catalyses the conversion of pyruvate to OAA. Males with PDH or homozygous deficiency of PC present in the newborn period with a rapidly fatal hyperlactataemia. Females heterozygous for PDH deficiency may present with a dysmorphic malformation syndrome. Both PC and PDH can be assayed successfully in cultures of fibroblasts.

Oxidative phosphorylation is a remarkable intra-mitochondrial process responsible for producing the majority of the ATP required for normal cellular function. Five enzyme complexes (I to V) mediate OXPHOS activity. These complexes are made up of many different polypeptides; 13 of these are encoded in the mitochondrial genome and ~70 in the nuclear genome. Defects in any of these components may produce an OXPHOS disease. As would be predicted by the complexity of the system, OXPHOS disorders have a bewildering array of clinical presentations. These disorders should be suspected in any infant with hyperlacticacidosis with normal organic acids and a high lactate:pyruvate ratio in blood or cerebrospinal fluid.

Other IEM can present with high lactate levels. However this is a secondary phenomenon and can be easily diagnosed by the presence of abnormal organic acids.

Fatty acid oxidation defects

Mitochondrial FAOD most commonly present in later infancy or childhood but may be apparent in the neonatal period. The three major clinical phenotypes associated with FAOD are hypoketotic hypoglycemia, cardiomyopathy, and myopathy. This group of disorders can thus present in several of the modes discussed in other sections. These disorders are now best diagnosed by blood spot acylcarnitine profile determined by tandem mass spectrometry, with subsequent specific enzyme assay in fibroblasts.

The common diagnoses in this group are:

- Medium chain acyl-CoA dehydrogenase deficiency which causes recurrent hypoketotic hypoglycaemia and can be rapidly lethal in the neonatal period if not recognised.
- Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency which may cause severe multiorgan failure with high morbidity and mortality.
- Mitochondrial TFP deficiency may cause severe neonatal cardiomyopathy and early death.

PROMINENT VISCERAL INVOLVEMENT

Isolated visceral involvement as a neonatal presentation of IEM is relatively rare. The two organs most commonly involved are the liver and the heart. Cholestatic jaundice can be the presenting symptom in α1-antitrypsin deficiency and inborn errors of bile acid metabolism. Hepatomegaly with generalised liver failure suggests tyrosinaemia type I, galactosaemia, neonatal haemochromatosis, or respiratory chain disorders. Hepatomegaly with hypoglycaemia is the usual presentation of glycogen storage disorders. Hepatosplenomegaly in the newborn period is rare but may be seen in GM1 gangliosidosis, Gauchers disease, Niemann–Pick disease, and Wolman disease. Cardiomyopathy can be a presenting problem in respiratory chain disorders, fatty acid oxidation disorders, and glycogen storage diseases.

THE FLOPPY BABY (+/- SEIZURES)

Profound central hypotonia is an unusual, but highly characteristic, presentation of IEM. This clinical picture is usually present from birth and is often associated with seizures and other neurological abnormalities and usually rapidly causes death. This presentation probably reflects prenatal cerebral damage and/or malformation. The 'common' diagnoses in this group are:

- Disorders of peroxisomal function Zellweger (cerebro-hepato-renal) syndrome autosomal recessive disorder associated with a generalised disorder of peroxisomal function (i.e. interrupting peroxisome assembly) or single matrix enzyme

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deficiency. Most present with profound congenital hypotonia and no psychomotor development. Hepatomegaly is seen in ~80%, renal cortical cysts in ~70%, sensorineural hearing impairment in ~90%, and abnormal ERG in ~85%. The main radiological finding is calcific stippling of the patellae and synchondrosis of the acetabulum. The birth prevalence is between 1 in 25,000 and 1 in 50,000 live births. Elevated ratios of both C24:0/C22:0 and C26:0/C22:0 in all tissues is used for diagnosis.

- Menkes disease is a rare X-linked disorder of copper transport. The clue to this diagnosis is in the steely appearance of the hair (pili torti) in affected individuals. The causative gene has been cloned and the predicted protein (termed ATP7A) has features characteristic of the family of cation translocating membrane proteins termed P-type ATPases.

Congenital hyperlacticacidaemias may also present in this way although they more commonly present as intoxications. The non-IEM differential diagnoses include sepsis, birth asphyxia, CNS malformations, Prader–Willi syndrome, chromosome abnormalities, and transplacental exposure to medications.

THE BABY WITH MALFORMATIONS

Major malformations are present in ~2·5% of births. The cause of the majority of these birth defects is not known. Rarely, IEM can present as isolated CNS malformations or multiple malformation syndromes. Apart from the peroxismal disorders mentioned above, the two main groups are:

- *Cholesterol biosynthesis disorders.* Smith–Lemli–Opitz syndrome (7-dehydrocholesterol reductase deficiency) is an autosomal recessive condition characterised by microcephaly, cleft palate, cardiac malformations, polydactyly, genito-urinary anomalies, and 2/3 syndactyly. Low serum cholesterol with the accumulation of 7-dehydrocholesterol is diagnostic.
- *Congenital disorders of glycosylation.* These are a group of rare autosomal recessive disorders characterised by hypotonia, cerebellar hypoplasia, and abnormal fat distribution. The diagnosis is usually made on the finding of abnormal glycosylation in serum transferrin.

THERAPIES FOR INBORN ERRORS OF METABOLISM

A detailed discussion of therapeutic approaches in IEM cannot be given here and can be found in Scriver *et al.*[2] A metabolic specialist should be involved as early as possible in these cases. However the general principles of emergency therapy are:

- Correct acid–base balance.
- Remove/reduce source of intoxicating compound (e.g. dietary protein).
- Replace deficient product.
- Remove toxic intermediary compound (e.g. haemodialysis or exchange transfusion).
- Provide co-factors for deficient enzyme.
- Provide alternative pathways.
- Provide enzyme replacement (e.g. transplantation or infusion of recombinant enzyme).

Some specific approaches are:

- *Aminoacidopathies.* Restrict natural protein and provide appropriate synthetic amino acid mixes.
- *Organic acidurias.* Restrict protein and provide appropriate synthetic amino acid mixes. Carnitine can be useful to facilitate renal excretion of abnormal intramitochondrial metabolites.
- *Hyperammonaemias.* Restrict natural protein and provide alternative pathways of nitrogen removal, e.g. phenylbutyrate. Liver transplantation can be useful.
- *Congenital hyperlacticacidaemias.* Often difficult to treat but may respond to cofactors such as biotin, riboflavin, and ubiquinone. Dichloroacetic acid can be used to stimulate lactate removal in some circumstances.

CONCLUSION

Over the last 50 years, the study of genetic biochemical disorders has been a very fruitful area of scientific endeavour. It has been particularly gratifying that this research has enabled the elucidation of normal human biochemical processes. Making a biochemical diagnosis in the perinatal period may allow effective treatment regimens to be instituted and also clarifies the genetic risk for subsequent pregnancies with access to accurate prenatal diagnosis.

KEYPOINTS

- Inborn errors of metabolism are individually rare but collectively common.
- Successful treatment requires early diagnosis.
- A few screening investigations can detect the majority of inborn errors of metabolism. These 'screens' should be directed by the type of presentation, e.g. in acute intoxication screen for blood glucose, lactate, ammonia, and full amino acid and acyl carnitine profile with urinary organic acids profile.
- Do not delay investigations of inborn errors of metabolism until sepsis has been excluded.
- Involve a specialist in inborn errors of metabolism as early as possible in the investigation of complex cases.

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FURTHER READING

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