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Metabolic acidosis in newborn infants

The maintenance of a proton (hydrogen ion) concentration within a relatively narrow range is essential for normal cellular function. This is as true for newborn infants as it is for older children and adults. Although very large quantities of protons are produced during normal metabolism by the oxidation of substrates to carbon dioxide, hydrolysis of adenosine triphosphate and reduction of adenosine dinucleotides, these are effectively removed by associated reactions. In health net production of protons results primarily from the catabolism of sulphur-containing amino acids and hydrolysis of nucleic acids in the diet. In order to maintain a normal pH, hydrogen ions are buffered by extracellular and intracellular proteins, inorganic phosphate, and bicarbonate. Net loss of protons from the body results from loss of carbon dioxide in expired gas (with hydrogen ions being effectively lost to water) and from the excretion of dihydrogenphosphate and ammonium ions by the kidney. Reabsorption of sodium bicarbonate by renal tubules, although not resulting in any net loss of protons, is also important in maintaining normal acid-base balance.

Respiratory acidosis in the newborn period may be due to disorders such as respiratory distress syndrome, transient tachypnoea of the newborn, and meconium aspiration, and results from the reduction in carbon dioxide excretion by the lungs with a subsequent increase of carbonic acid. Metabolic acidosis, defined as the accumulation of non-carbonic acid equivalents, arises from excessive production or inadequate excretion of hydrogen ions or from an increased loss of bicarbonate. In practice metabolic acidosis may result from birth asphyxia, cold stress, hypovolaemia, sepsis, congenital heart disease (particularly hypoplastic left heart syndrome, coarctation and interruption of the aortic arch), renal disease (for example polycystic kidneys, obstructive nephropathies, renal tubular acidosis), maternal acidosis, and inborn errors of metabolism.¹ Acidosis has also been reported in newborn infants with imperforate anus and rectovaginal fistula,^{2,3} neonatal diabetes,⁴ benzyl alcohol poisoning,⁵ saline flushes,⁶ parenteral nutrition,⁷ and in those fed with casein formulas⁸ or with goats' milk.⁹

Although the mechanisms by which acidosis causes harm are not fully understood, severe acidosis is associated

with disturbances in cerebral blood flow, periventricular haemorrhage, leucomalacia, increased peripheral vascular resistance, and decreased myocardial function.^{10,11} A fall in cardiac output and poor tissue perfusion may increase tissue hypoxia and lead to worsening acidosis.

Preterm infants are more susceptible to many disorders that cause metabolic acidosis such as cold stress, infection, and respiratory distress syndrome and have a reduced capacity to prevent and correct acidosis. Although the kidneys will respond to an acid load in a qualitatively similar manner to term infants, immaturity of renal function results in a reduced glomerular filtration rate, lower tubular bicarbonate threshold, and increased urinary sodium loss.¹² Additionally any concomitant respiratory disease may restrict the ability of the preterm infant to compensate for a metabolic acidosis by increasing the excretion of carbon dioxide.

Inborn errors of metabolism

Although individually uncommon, inborn errors of metabolism are not a rare cause of metabolic acidosis in the newborn and are more likely where there is consanguinity or a family history of unexplained neonatal deaths or illness. Their presentation is, however, usually non-specific, and unless appropriate investigations are undertaken the correct diagnosis may be missed. Characteristically, but not exclusively, infants with an inborn error of metabolism are born at term and are initially well. In preterm infants acidosis is much more likely to be secondary to other causes such as septicaemia but the possibility of an inherited metabolic disorder should still be borne in mind. The main groups of inborn errors that may present with a severe metabolic acidosis are (i) defects of pyruvate metabolism and the mitochondrial electron transport chain, (ii) the organic acidurias, and (iii) defects of gluconeogenesis.

Investigations

In the majority of sick infants a full infection screen and liver function tests will usually be undertaken and concentrations of arterial blood gases, blood glucose, and

plasma electrolytes are measured. A metabolic acidosis is evident from a low plasma bicarbonate, a low arterial carbon dioxide tension, and a low arterial pH. The history, clinical examination, and the results of these initial investigations will normally be sufficient to determine the cause or to indicate which additional investigations are necessary. In infants where the acidosis is unexplained, particularly severe, or persistent, or where there is a large anion gap, the possibility of an inborn error of metabolism should always be considered and further investigations should then include measurement of concentrations of blood lactate and ammonia, plasma amino acids and urine amino acids, organic acids, ketones, and reducing substances. Assays on specific tissues samples will be dependent on the results of these. A directory of laboratories in the UK and Northern Ireland undertaking specialised metabolic investigations is available.¹³

Lactic acidosis

Although a raised blood lactate concentration is most often secondary to tissue hypoxia it is also found in inherited disorders of hepatic gluconeogenesis (glucose-6-phosphatase deficiency, glucose-6-phosphate translocase deficiency, and fructose-1,6-bisphosphatase deficiency), disorders of pyruvate metabolism (defects in the pyruvate dehydrogenase complex and pyruvate carboxylase deficiency), and functional defects in the mitochondrial electron transport chain. It may also be associated with organic acidaemias. Gluconeogenic disorders are associated with hypoglycaemia. In congenital lactic acidaemias symptoms may be apparent from birth, the blood lactate concentration is usually above 5 mmol/l, and an anion gap is present that may be accounted for by the hyperlacticacidaemia. In contrast to lactic acidosis secondary to tissue hypoxia, ketosis is present and the acidosis persists even when there is adequate cardiac output and tissue perfusion.¹⁴ Infants with pyruvate dehydrogenase deficiency may be dysmorphic.¹⁵ The biochemical diagnosis of these disorders, and interpretation of results, is particularly complex and undertaken by only a few specialised laboratories. Despite significant advances in the investigation of infants with congenital lactic acidosis in many the underlying metabolic abnormality remains unknown.

Organic acidaemias

Most children with an organic acidaemia are born at term and are well for the first one to four days of life. The onset of illness is not necessarily related to the start of feeding but may be triggered by endogenous protein catabolism. There is then a rapid deterioration beginning with poor feeding, irritability, and lethargy proceeding to apnoea and coma. On examination there may be dehydration, respiratory distress, central hypotonia, and limb hypertonia. Initial investigations will show a severe metabolic acidosis, ketosis, and usually hyperammonaemia and hypocalcaemia. Neutropenia, thrombocytopenia, and hypoglycaemia or hyperglycaemia are often found. The most common of the organic acidaemias, propionic, methylmalonic, and isovaleric acidaemia all present in this way, although variants with residual enzyme activity may not become unwell until later. Other rarer organic acidaemia in which metabolic acidosis may occur in the newborn period include 3-methylcrotonyl CoA carboxylase, 3-hydroxy-3-methylglutaryl CoA lyase, holocarboxylase synthase, electron transfer protein (ETF) or ETF:ubiquinone oxoreductase,

succinyl CoA:3-ketoacid CoA transferase, and glutathione synthetase deficiency. Maple syrup urine disease (keto acid branched chain decarboxylase deficiency) is often through to present with metabolic acidosis but this is rarely significant, although ketosis is generally found.¹⁶ The diagnosis of an organic acidaemia is made by finding characteristic organic acids in the urine on analysis by gas chromatography linked to mass spectrometry (GCMS). This investigation is now available in most regional centres and a collection of urine for GCMS should be routine for all infants with an unexplained metabolic acidosis.

Other inherited metabolic disorders may also be associated with acidosis – for example salt losing forms of congenital adrenal hyperplasia (21-hydroxylase, 3 β -hydroxysteroid dehydrogenase, and 20,22 desmolase deficiency). Metabolic acidosis may be found in galactosaemia (as a consequence of renal tubular acidosis) but liver failure is likely to be predominant. Urea cycle disorders are often initially associated with a respiratory alkalosis, however, as infants deteriorate acidosis may develop.¹⁷

Treatment

The treatment of neonatal metabolic acidosis consists of general supportive care and specific measures dependent upon the cause. Treatment of hypothermia, hypovolaemia, hypoxia, and electrolyte disturbances will usually correct metabolic acidosis secondary to asphyxia or poor tissue perfusion. Intravenous antibiotics should be given until sepsis has been excluded. Many infants will require ventilatory support. The morbidity and mortality for those infants with potentially treatable disease is likely to be significantly improved by skilled neonatal intensive care. The use of intravenous sodium bicarbonate to correct metabolic acidosis is controversial. There have, however, been no prospective trials of its use in newborn infants. It is considered by some to be unnecessary and even harmful, leading to changes in cerebral blood flow and paradoxically to increased cerebrospinal fluid or intracellular acidosis,¹⁸ although provided that carbon dioxide can be effectively removed in expired air (by assisted ventilation if necessary) it will lead to a net loss of protons to water. If bicarbonate is used then it is important that the infant's ventilation is adequate, and hyperosmolar solutions should be diluted 1:2 to 1:4 with water and infused slowly over several minutes. In inborn errors of metabolism acidosis may lead to continued protein breakdown with further accumulation of toxic acidotic metabolites and sodium bicarbonate should be given. Glucose infused at a rate of up to 10 mg/kg/minute may inhibit protein catabolism in babies with inborn errors of metabolism and this effect will be further augmented by the addition of a continuous infusion of insulin, starting at 0.01 U/kg/hour, provided that the blood glucose concentration is satisfactory. In order to give sufficient glucose, but to prevent overhydration, particularly where there is renal impairment, concentrations in excess of 10% may be necessary. These are irritant to peripheral veins and should, if possible, be given via a central venous catheter. There are, however, limitations on the quantity of fluid that can be safely given and hypernatraemia may result from large quantities of sodium bicarbonate infused. In such cases it may be necessary to use peritoneal dialysis, haemodialysis, or haemofiltration to remove toxic metabolites and fully correct the acidosis.¹⁹⁻²¹

A number of inborn errors of metabolism are partially or wholly corrected by treatment with pharmacological

amounts of the specific cofactors, but with the exception of holocarboxylase synthase deficiency where biotin should be given, those presenting acutely in the newborn period are unlikely to be responsive. The infusion of L-carnitine (up to 50 mg/kg/hour during acute illness) has been shown to increase the removal of toxic acyl CoA metabolites in patients with organic acidaemias,²² but the high production rate of these metabolites may be far in excess of the infused carnitine,²³ and the efficacy of carnitine treatment in acute metabolic decompensation remains unproved. In isovaleric acidaemia, glycine (250–500 mg/kg/day) significantly increases the excretion of isovalerate as isovaleryl-glycine.²⁴

Conclusion

Metabolic acidosis is common in the newborn infant. It is most often secondary to disorders resulting in hypoxia or poor tissue perfusion and will be corrected by the appropriate treatment for these conditions. It is, however, important for those caring for newborn infants to be aware that metabolic acidosis may be a result of an inborn error of metabolism and for specific investigations to be undertaken earlier rather than later. A correct diagnosis is important not only for appropriate treatment to be given but also to allow genetic advice to be offered to families including prenatal diagnosis for future pregnancies.

J H WALTER

Willink Biochemical Genetics Unit,
Royal Manchester Children's Hospital,
Pendlebury, Manchester M27 1HA

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