Personal practice

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Management of newborn babies in whom serious metabolic illness is anticipated*

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The problem under discussion is best described by an illustrative example. A woman was referred for advice and management midway through her fourth pregnancy. She had one healthy son, her third born. Her first two babies (1 male, 1 female) had both died on the third day of life. Each had seemed normal at birth, but had become drowsy on the second day and then unconscious. She had already decided that there must be a high risk of a similar occurrence in this pregnancy, but she wanted the pregnancy to continue whatever the risk. She hoped we might be able to diminish the risk by some means.

Autosomal recessive inheritance of some metabolic disease was suspected. Information about the babies who died revealed only that they did not die of hypoglycaemia, hypocalcaemia, cerebral haemorrhage, or gross cerebral malformation.

The task set us by this woman was therefore the management of a newborn baby who was believed to have a 1 in 4 risk of suffering from a rapidly fatal inborn error of metabolism of unknown type. This clinical problem confronts our unit two or three times each year and this paper describes the plan of management developed.

The unit has been working on inborn errors of metabolism for the last 3 years. Though we are primarily interested in searching for new inborn errors, we also provide a diagnostic service for the known inborn errors in the State of Victoria (75,000 births per year). The laboratories are situated in the Royal Children's Hospital, which cares for about 80% of severe childhood illness in the state. There is a close liaison with the Royal Women's Hospital (9000 deliveries per year) and the Queen Victoria Hospital (6000 deliveries per year).

Plan of management

The baby is delivered by the practitioner looking after the mother's pregnancy at a hospital of his choice, provided that transfer to the Royal Children's Hospital can be arranged promptly after birth. Labour is induced early on a Monday morning at or very near term, because it is unrealistic to claim that a full range of laboratory procedures is as available over the weekend as during working days. The baby is fed glucose to the limit of gastrointestinal tolerance (generally 7% initially, building up to 7% glucose+7% glucose polymer†) while investigations are carried out, because most of the rapidly fatal inborn errors of metabolism are aggravated by protein load and by tissue catabolism. Cord blood is collected and blood is obtained on admission and at 24 hours of age. All urine passed in the first 24 hours is collected and each sample is frozen promptly. The tests employed include high voltage electrophoresis of urine and of serum amino acids, backed up by column chromatography when necessary; gas-liquid chromatography of ethyl acetate/ether extractable organic acids in urine; measurement of ammonia, urea, glucose, sodium, potassium, chloride, calcium, phosphorus, magnesium, and acid-base analysis of blood.

Results of all these tests are made available within 12 hours. Consequently, most of the serious known inborn errors of metabolism can be diagnosed or excluded before the baby is 48 hours old.

If the results are normal, and the baby is well, protein-containing feeds are then introduced cautiously over the next 48 hours and urine studies are continued throughout this period. Blood ammonia estimation and high voltage electrophoresis of serum amino acids are repeated at the end of this

*In the 'Personal practice' series of articles authors are invited to give their own views on some current practical problem.

†Caloreen.

second 48 hours, or earlier if some clinical indication develops.

Using this regimen, a normal baby whose investigation turns out (in retrospect) to have been unnecessary will be established on a normal protein intake by the age of 4 days and will have had a venous blood sample taken on only two or three occasions.

Diagnosis of a known inborn error of metabolism leads immediately to institution of the appropriate method of treatment—if one exists.

Some babies may become ill or develop serious abnormalities in laboratory tests without the tests revealing the underlying cause. In this circumstance we use a series of empirical therapeutic measures in addition to symptomatic treatment (e.g. correction of hypoglycaemia, hypocalcaemia, or acidosis, and ventilatory assistance).

(1) Provision of calories at, or in excess of maximal estimated requirement, as dextrose—this generally means 20% dextrose intravenously. This is done to minimize catabolism, and on the assumption that a defect may exist in the metabolism of fat or protein.

(2) Parenteral administration of pharmacological (100 to 1000 times physiological) doses of all those vitamins which are free of toxic effects in the short term—pyridoxine, thiamine, riboflavin, nicotinic acid, vitamin B_{12}, folic acid, and ascorbic acid. The known vitamin dependency states (Rosenberg, 1969) provide the argument for this step.

(3) Exchange transfusion is employed if clinical and/or serious biochemical deterioration occurs despite the above measures, on the assumption that it may remove toxic metabolites. If a definite improvement is achieved this procedure is repeated once, or exceptionally, twice. It is used merely to buy time to allow a more permanent way of controlling the metabolic fault to be found.

Results

This plan has been used in 6 babies. 4 proved to be normal. 3 of these were sent home on normal feedings on the fifth or sixth day. 1 baby was shown to have a slightly raised level of blood ammonia (180 μg/100 ml) and was treated with a restricted protein intake for 10 days before being discharged breast fed. He subsequently proved to have normal protein tolerance.

The most successful case is described elsewhere in this issue (Danks, Tippett, and Zentner, 1974). The past obstetric history of that case was used above to introduce this paper. The diagnosis of citrullinaemia was made by 24 hours of age. Treatment by protein restriction from birth has been very successful and his normal clinical condition at 6 months of age contrasts with the deaths of his sibs and of all 3 acutely ill babies previously described with this condition.

The last baby was born to a woman with 4 healthy children whose last 3 successive babies had died of acute hepatic necrosis in the first fortnight of life. Acidosis and hypoglycaemia had been the first abnormalities in each baby.

The baby studied was already acidotic and hypoglycaemic at 4 hours of age. The regimen described was started promptly. Exchange transfusion was employed at 18 hours of age, partly because the serum bilirubin was rising rapidly. He then progressed well for 5 days during which he was weaned off intravenous dextrose onto oral dextrose, and then oral dextrose plus medium chain triglyceride oil.

On the second day after the fat was started (day 7), acidosis, drowsiness, and a remarkable red, raw tongue developed. The massive doses of vitamins had been reduced to near physiological levels when the intravenous catheter had been removed on day 5. Intravenous dextrose was restarted along with large intravenous doses of vitamins B_1, B_2, B_5, and B_6. The tongue healed dramatically in the next 24 hours, but the baby lapsed into liver failure and died on day 14. Necropsy revealed massive acute hepatic necrosis. It seems possible that the basic disease was concerned with a need for huge doses of riboflavin—a riboflavin-dependency state.

Discussion

Ultimately, one might hope that this type of problem would disappear from neonatal paediatrics. First affected babies in families would still occur unexpectedly, but, in the future a precise diagnosis would be reached in every case and subsequent pregnancies could then be handled with confidence, using intrauterine diagnostic procedures or prompt and specific investigation after delivery.

For many years to come we will have to deal with families whose previous babies have died undiagnosed and it is useful to have a plan of management ready long before the new baby is born. The procedures outlined above will not harm a normal baby. The mother-baby separation involved is unfortunate, but not as important as it might seem, because mothers in this situation often refuse to see their new baby until someone can guarantee that he/she is not going to die. All mothers with this problem seem to hold back from deep emotional involvement with the baby until their anxiety fades with the passage of days or weeks. Consequently the plan outlined may even hasten the establishment

of a good mother-baby relationship by allowing early and confident reassurance. All the parents we have dealt with have expressed relief that the anxiety of waiting to see what will happen has been taken off their hands.

Colleagues have expressed fear that our active therapeutic endeavours will keep alive brain damaged babies. This risk is, of course, present in every form of active treatment in paediatrics and especially in the newborn period. If we use our active treatment with discretion we should be able to minimize the occurrence of second-rate survival. It is for this reason that the plan expresses caution about repeated exchange transfusions. This procedure is very useful to tide babies over the difficult phase of early postnatal catabolism, but some simple form of treatment must be found if first-rate survival is to occur. The use of common sense and critical review of what the treatment is achieving in a particular baby can still allow the natural course of events to proceed in untreatable diseases.

The range of tests we use is clearly inadequate to cover all possible inborn errors of metabolism. We plan to add gas-liquid chromatography of short chain fatty acids and paper chromatography of amines to the repertoire shortly, and we are also working up mass spectrometry methods in gas-liquid chromatography.

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