PERSONAL PRACTICE

Early recognition of metabolic decompensation

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Many inherited metabolic diseases are complicated by episodes of decompensation and encephalopathy. These may be precipitated by catabolism, such as that associated with infections but in some cases, no acute precipitant is apparent. The clinical signs vary from one child to another but generally include abnormal behaviour, drowsiness, and a glazed look. Prompt intervention is essential if long term neurological sequelae are to be avoided. In a previous article, we have outlined our strategy for the initial management of such episodes.[1] Here we consider the relative value of clinical signs and biochemical tests for the detection of decompensation.

Fatty acid oxidation defects

In fatty acid oxidation defects, fasting can precipitate severe encephalopathy. The mechanism of this is not fully understood: high circulating non-esterified fatty acids, low glucose, and relatively low ketone concentrations all appear to contribute. Measurement of blood glucose concentrations is sometimes recommended during intercurrent illnesses as a guide to management.

In our experience, unfortunately, it is of limited value and can even be dangerous. There are two reasons for this. Firstly, blood glucose monitoring at home can only be done with reagent sticks and reflectance meters. The sensitivity of these is poor in the lower part of their range, even when performed regularly by experienced staff. Occasional measurements by parents cannot distinguish reliably between concentrations of 2.5 and 3.0 mmol/l, which would be necessary for the test to be useful. Secondly, though blood glucose concentrations fall progressively with fasting, hypoglycaemia (glucose <2.6 mmol/l) is a relatively late finding in β-oxidation defects: most patients become unwell long before they are hypoglycaemic. Delaying admission until the blood glucose is low can, therefore, be dangerous. Plasma fatty acid concentrations would be a better biochemical marker of incipient decompensation but analysis is not currently available as an urgent investigation. Fortunately, it is relatively easy to manage episodes of acute illness clinically. An emergency regimen should be instituted as soon as patients become unwell, with frequent drinks of carbohydrate polymer.[1] Admission should be arranged for an intravenous glucose infusion if they vomit persistently, become encephalopathic, or fail to improve promptly.

Glycogen storage disease type I

In glycogen storage disease type I, hypoglycaemia occurs early, after as little as two hours of fasting. Moreover, patients with long standing poor biochemical control may remain completely asymptomatic, presumably because they are using alternative fuels, such as lactate.[2] One might, therefore, expect blood glucose monitoring to be helpful in deciding when to institute emergency management. In practice, even in this condition, we find blood glucose monitoring of little use. Any illness should trigger use of the emergency regimen, regardless of the blood glucose concentration, and the need for admission will be determined by clinical factors, such as vomiting, drowsiness, or tachypnoea (suggesting acidosis). Indeed, detection of very low blood glucose concentrations in an asymptomatic child is liable to induce inappropriate panic.

Organic acidaemias

Decompensation in propionic and methylmalonic acidaemias is often accompanied by acidosis, but this is not always the case. The plasma ammonia concentration and the presence of ketones in the urine are more reliable markers of acute decompensation. Plasma ammonia is now widely available as an urgent investigation, while ketonuria has the advantage of being detectable by parents at home. In severely handicapped children, who are difficult to assess, analysis of a urine specimen every morning is sometimes recommended as it may alert parents to an unsuspected illness or help them to decide when the child needs admission. In our experience, however, parents quickly become skilled at detecting the clinical signs of decompensation and the response to the emergency regimen will determine the need for admisssion.

Maple syrup urine disease

In maple syrup urine disease, decompensation may be associated with no abnormalities on routine biochemical tests. Thus, even when the patient is severely encephalopathic, blood pH, glucose, lactate, and ammonia concentrations are usually normal and there may be no ketosis. Patients' urine may have an abnormal odour but this is a late and unreliable finding.

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Frequent monitoring of plasma branched chain amino acids is part of the routine management in maple syrup urine disease. High levels indicate patients at risk, and adjustment of the branched chain amino acid intake undoubtedly prevents many episodes of decompensation. Unfortunately, as the branched chain amino acid results are not immediately available, they cannot help in the initial management of an acute deterioration, such as that precipitated by infection. Instead, drowsiness, unsteadiness, or subtle behavioural changes detected by the parents should prompt appropriate dietary modification. Measurement of branched chain amino acids is essential for management during the recovery phase, as concentrations of the three amino acids do not necessarily fall synchronously. Very low concentrations of one amino acid will slow recovery, and supplements of individual branched chain amino acids should be given when required.

Urea cycle disorders
Hyperammonaemia is the principal cause of neurological damage in urea cycle disorders and the maximum level of ammonia during an episode of decompensation correlates broadly with the likelihood of subsequent impairment. Levels may, however, be normal initially and later rise rapidly, so the ammonia concentration at presentation is not always a reliable guide to the intervention required. Once again, the child's clinical state is a better guide to the immediate clinical management.

Since glutamine acts as a 'buffer' for ammonia, knowledge of the glutamine concentration facilitates interpretation of the ammonia result.[3] High glutamine concentrations indicate that a patient is at risk of hyperammonaemia and requires a lower protein intake or increased doses of drugs that promote nitrogen excretion (sodium benzoate or sodium phenylbutyrate). Thus, routine glutamine measurement can allow incipient decompensation to be averted. Unfortunately, glutamine concentrations, like those for branched chain amino acids, are not immediately available and cannot help in the acute situation.

Conclusions
Clinical observations are generally better than biochemical measurements for detecting decompensation in disorders of intermediary metabolism. Subtle changes in behaviour are usually the earliest signs and are most readily detected by the child's parents. Medical staff being less sensitive to these signs, often prefer objective evidence, such as measurements of blood glucose, pH, or ammonia. We think parents should be encouraged to trust their clinical judgment, especially as some tests, notably the monitoring of blood glucose concentrations, can be unreliable. Parents should also be encouraged to make decisions, initiating emergency management at home. These measures will avoid any delay in treatment, reduce hospital admissions and improve the parents' self confidence.

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2 Fernandes J, Berger R, Smit GP. Lactate as a cerebral metabolic fuel for glucose-6-phosphatase deficient children. *Pediatr Res* 1984;**18**:335-9.
3 Maestri NE, McGowan KD, Brusilow SW. Plasma glutamine concentration: a guide in the management of urea cycle disorders. *J Pediatr* 1992;**121**:259-61.