Think metabolically

Editorial

There are several hundred inherited metabolic diseases in McKusick's latest edition of *Mendelian Inheritance in Man*[1], most of which deal with neurological problems. So how does the practising paediatric neurologist, let alone the paediatrician, make any sense of this? Good reviews on this subject exist, with the presenting features usually separated into age and symptom groups[2]. However, what should trigger the practitioner to consider that the neurological disease is metabolic?

Traditionally, we have tended to think of slowly progressive diseases as being lysosomal, and intermittent or recurrent problems as being due to aminoacidopathies or organic acidurias, but recently the picture has widened. Neonatal and infantile encephalopathies may be ascribed to hypoxia/ischaemia or a viral origin when in fact they represent an acute decompensation due to an amino acid disorder or an organic aciduria precipitated by fasting or feeding. Infants with developmental delay and dysmorphism, even with migrational disorders, may have peroxisomal defects, and those with clear cystic malformations of the brain on MRI may have non-ketotic hyperglycinaemia. Subdural effusions may be a feature of glutaric aciduria.

It has been said that children with disorders of respiratory chain function may present 'acutely, subacutely or chronically with symptoms related to any system or in any combination' (personal communication). While this may be true, in practice one needs to have a high index of suspicion and be selective about children with unknown myopathy, especially if associated with fatigue, cardiomyopathies, ophthalmoplegias, recurrent vascular episodes, and myoclonic epilepsy, or with neurological symptoms and lactic acidosis. Recurrent episodes of ataxia or coma, usually triggered by infection, may not be easily diagnosed as metabolic because all tests are often normal during stable or 'interictal' periods. Therefore, the tests should be performed on blood and urine during one of the decompensating episodes.

Some children with apparently severe static delay may have been developing normally and then deteriorated in infancy, but this aspect of the history may have been missed, giving rise to a non-progressive picture of severe learning disabilities and spasticity; I have seen this with late infantile Batten disease. Others may have diseases misdiagnosed as cerebral palsy, which are so slowly progressive that the degenerative nature of the condition is not noted until teenage years. Ataxia telangiectasia due to a DNA repair defect or Dopa-sensitive dystonias can present in this way. Lethargy and depression may herald Wilson's disease in the older child. Van der Knaap and colleagues[3] have described the unusual picture of a chronic often stepwise leukodystrophy, with episodes triggered by infection or trivial head injury.

Adult neurologists, too, must be aware of the range of metabolic disorders that may present, apparently, for the first time in adult life. Adrenoleukodystrophy presenting as severe learning disabilities, Niemann–Pick C disease with ataxia, and glutaric aciduria with dystonia have all been recorded. A family history of not only similar but also unrelated problems may indicate metabolic disorders; for example, a family history of migraines, sudden death, and episodes of ataxia in the relatives of a child with headache and papilloedema gave a clue to the diagnosis of a urea cycle defect in one of my patients.

Recently, we have become aware that Smith–Lemli–Opitz syndrome, while apparently static, is due to a disorder of cholesterol metabolism. Strokes may be of metabolic origin, and carbohydrate-deficient glycoprotein syndrome may show a variety of features dependent on the age at presentation, including wasting and failure to thrive, ataxia and developmental delay.

A new concept is that a defect in the glucose transporter protein (GLUT 1) may present with mild delay, microcephaly, and epilepsy, and may respond to a ketogenic diet[4]. A low CSF glucose in the presence of a normal blood glucose is important in confirming this disease, which may be more common than we realize. MRI scanning and spectroscopy could be helpful in supporting a metabolic diagnosis, but sometimes the signs are subtle and not always specific[5]. A good history and clinical examination together with a thoughtful approach and a knowledgeable biochemist are essential to achieve a high level of positive diagnoses.

It behoves us in these days of clinical audit, whether by the National Institute of Clinical Excellence in the UK or the Health Maintenance Organization in the USA, to be cost-effective in our diagnostic procedures and not have a 'blunderbuss' approach. However, we also have a duty to children with disabilities and their carers to make or exclude a neurometabolic diagnosis, although this may take time and require follow-up, and to be able to advise on prognosis, genetic management and, although rarely, specific therapies. The balance is difficult and is known as the Art of Medicine.

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References

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