Biochemical genetics: what do you need to know?

Clinical chemistry is a frontline facility when dealing with the diagnosis of metabolic disorders. Here, George Gray, Mick Henderson and Mark de Hora provide guidance on how to spot such conditions and give an overview of what assistance is available to the routine laboratory.

Biochemical genetics is the study of the influence of genes on biochemical pathways. In the context of clinical biochemistry, this means a study of inherited metabolic diseases or inborn errors of metabolism. They are single gene disorders that follow Mendelian inheritance. Individually, they are rare but, because there are so many genes involved in metabolic pathways, a substantial number of patients are diagnosed each year with a metabolic disease. Some may present at birth, and some not until adulthood, while others may only show clinical symptoms if they are exposed to trigger factors.

The crucial thing is to 'think metabolic' and to recognise when the pattern of symptoms and biochemical results could indicate a metabolic condition. More and more of these disorders are now treatable and in many cases a delay in treatment can leave the patient with irreversible residual damage. In addition, by identifying one member of a family with a genetic condition, you can then offer counselling and in many cases antenatal diagnosis to the parents, and you may also identify other affected or at-risk family members.

There are specialist centres for diagnosing these disorders in all regions of the country, and these are organised as a network (MetBioNet), supplying advice and offering testing. However, the front line for the diagnosis of metabolic disorders will always be the district general hospital and in particular the clinical chemistry laboratory.

WHAT CAN YOU DO?

How can the biomedical scientist in these laboratories help? There are hundreds of different disorders with dozens of different tests ranging from the commonplace to the downright exotic. Where does one start?

Symptoms

Certain symptoms raise the level of suspicion that a patient may have a metabolic disorder. Recurrent hypoglycaemia in a child should be investigated for a possible metabolic condition. The disorders we think about in this situation are glycogen storage diseases, fatty acid oxidation defects and disorders of gluconeogenesis. The patients may have lactic acidaemia and in some cases elevated plasma lipids.

Persistent metabolic acidosis that cannot be explained on the basis of septicaemia or organ shutdown is suspicious. The acidosis may be due solely to lactic acid, in which case a defect in pyruvate catabolism such as pyruvate dehydrogenase deficiency or a respiratory chain disorder may be the cause. Alternatively, it may be due to the accumulation of a variety of organic acids in blood and urine. In this case, analysis of urine organic acids and plasma acylcarnitines is essential.

Markedly elevated plasma ammonia in a patient without severe liver disease should always raise suspicion. If the patient is also acidotic then this may indicate an organic acid disorder. If there is no acidosis then it could be a urea cycle defect. A point to remember here is that plasma ammonia levels start to rise soon after collection so, unless the sample is analysed immediately or frozen immediately for analysis, it may be artefactual. If in any doubt, a repeat sample should be collected.

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A child showing dysmorphic features may have a chromosome abnormality or a genetic syndrome, but may also have a mucopolysaccharide storage disease or a defect of glycoprotein breakdown (oligosaccharidosis). They may also have skeletal problems and been investigated for bone disease. These can be diagnosed in urine by analysis of urine mucopolysaccharides (glycosaminoglycans) and oligosaccharides. Alternatively, the patient may have a disorder affecting a less-commonly considered organelle, the peroxisome. Such peroxisomal disorders often present with dysmorphic features, neurological symptoms and liver disease. Most can be diagnosed by measuring plasma very long chain (C26 and higher) fatty acids, which is performed in most specialist regional centres.

MetBioNet Biomedical Scientist Training Group

The MetBioNet Biomedical Scientist Training Group was set up in 2005. Its remit is to support specialist training for biomedical scientists working in laboratories undertaking metabolic testing and neonatal screening. The group comprises 10 scientists, nine biomedical scientists and the MetBioNet lead trainer, from laboratories across the UK. The organising group meets twice a year to plan meetings and develop resources. The group has also been collaborating with the IBMS to develop educational qualifications.

During the past four years the group has:

- established an annual symposium for biomedical scientists which takes place in the autumn
- developed workshops in laboratory techniques (eg gas chromatography mass spectrometry and enzyme analysis)
- developed a Diploma of Expert Practice in Bloodspot Newborn Screening in partnership with the Institute of Biomedical Science
- created web-based resources, presentations and links for biomedical scientists on the MetBioNet website – these are open-access and include contact details for specialist biomedical scientist staff in metabolic and screening laboratories
- worked with companies to provide affordable manufacturer training on specialised scientific equipment.

If you would like further information about planned activities or would like to speak to one of the group regarding training of biomedical scientists, please contact Mark de Hora (tel 0117 323 5556) or Barbara Waddell (tel 0113 206 4256). Alternatively, further information on the group's activities is available on the website (www.metbio.net/metbioBMSTrainingGroup.asp).

A big liver and spleen (hepatosplenomegaly) can be a result of an infection or cancer but can also be a symptom of a lysosomal storage disease. Gaucher's disease and Niemann-Pick disease types A, B and C are defects of the breakdown of complex lipids in the lysosome that can present in this way. Apart from Niemann-Pick type C, diagnosis is by measurement of enzymes in leucocytes.

Untreated children with neurological disease due to lysosomal storage in the brain show regression. This means that while initially they may progress and develop skills, they eventually plateau and lose the skills they acquired. This pattern is often an indicator of this type of metabolic disease.

Finally, many metabolic diseases show a renal tubulopathy. Often this is a reflection of the fact that reabsorption in renal tubular cells is energy-dependent, and defects of energy production such as disorders of the respiratory chain can compromise this function.

Scanning test results

Many analytes measured routinely in district general hospital laboratories can be abnormal in metabolic conditions and sometimes scanning test results on a patient may lead to clues.

Often, cerebrospinal fluid (CSF) samples will be collected on patients with metabolic acidosis who have lactic acidaemia. Measurement of CSF lactate can often help to diagnose disorders primarily affecting brain lactate catabolism. A clearly raised CSF lactate in the face of a normal or only marginally elevated plasma lactate (collected at the same time) is strongly suggestive of a defect in brain pyruvate metabolism.

In addition to lactate, CSF glucose is often measured. The unusual combination of a normal plasma glucose (again taken at the same time) with a very low CSF glucose could indicate a defect in a brain glucose transporter that presents with seizures.

Most people worry about high plasma cholesterol but some patients with metabolic diseases can have low or undetectable cholesterol levels. These include abetalipoproteinaemia, where there is a defect in the absorption of lipids, and some of the peroxisomal disorders, where there is a defect in intracellular cholesterol biosynthesis. Raised plasma triglycerides are obvious clues to the lipoprotein disorders but they can also be elevated (along with cholesterol) in some of the glycogen storage diseases.

Plasma creatine kinase has long been used as a marker of muscle disease. Persistent and gross elevations are often diagnostic of a muscular dystrophy; however, if the elevations are intermittent, they may be due to metabolic myopathies such as long chain fatty acid oxidation defects or the muscle glycogen storage disease McArdle's syndrome.

Most laboratories measure plasma and urine uric acid. Elevations occur in a number of defects in purine metabolism, in particular Lesch-Nyhan syndrome, which presents in boys with severe neurological symptoms. Low levels are found in molybdenum co-factor deficiency (which presents with severe neurological symptoms early in life) and xanthinuria (which presents with kidney stones in adulthood).

The Metabolic Biochemistry Network website (www.metbio.net) lists all the laboratories in the UK, provides contacts details for clinical scientists and biomedical scientists in your nearby regional laboratory, and a list of tests that are available.

WHO DO YOU CALL?

There is a website for the Metabolic Biochemistry Network (www.metbio.net) that lists all the laboratories in the UK. You can find contact details for clinical scientists and biomedical scientists in your nearby regional laboratory, as well as a list of tests. All offer a core range of investigations, and what they do not offer they can forward to another member of the network. The website is also a very useful source of teaching material. It has diagnostic guidelines that can be helpful in various clinical situations.

WHAT CAN YOU DO FOR THE METABOLIC LABORATORY?

It goes without saying that it helps to give prior warning before collecting and sending perishable samples – particularly over weekends or on bank holidays. The laboratories do not routinely offer an out-of-hours service. It also helps to know how old the sample is and how it was stored, as well as whether the samples were taken after feeding or fasting.

When sending samples to other laboratories, many departments now transcribe the information onto a 'sending away' form and send this with the sample. There are many weird and wonderful names for the diseases we diagnose and an equally large number of strange-sounding tests. These can be difficult to read and interpret unless one is working in the field of metabolic disease. Hence, it is always useful to include a photocopy of the original request form along with the 'sending away' form.

Probably the most useful thing that you can do is to establish a dialogue with personnel in the regional laboratory, who can be an invaluable source of advice. Why not arrange to pay them a visit? You never know, you might come back inspired! ■

George Gray, Mick Henderson and Mark de Hora are MetBioNet trainers. This article is based on an invited presentation given at last year's Biomedical Science Congress.