

Diagnosis and Management Support for an Expanded Newborn Screening Programme

Janice M Fletcher,¹ MD, FRACP, FRCPA

Abstract

The introduction of tandem mass spectrometry technology expands newborn screening and permits early diagnosis of inborn errors of metabolism. Through measurement of a number of acyl carnitines, amino acids and associated ratios, infants at risk of inborn errors of metabolism can be detected. However the increasing availability of the technology places new challenges to areas with established programmes, as well as those without existing newborn screening programmes. Once the technical aspects of tandem mass spectrometry operation are overcome, the initial challenge lies in determination of whether a borderline result is abnormal. Participation in quality assurance and international collaborative programmes is critical to optimise sensitivity and specificity. Some conditions are readily detected, others are more problematic. All positive results must be confirmed with formal testing but the tests required will vary with the disorder. Even after confirmed diagnosis, the significance of the diagnosis for that child may not be clear, as mild forms of disorders, previously thought to be rare, are being recognised by newborn screening programmes. Parents should be provided with easy to understand written information and a management plan. Education of health professionals who may not be familiar with these conditions raises another challenge. Treatment should be supervised by an expert centre and outcome data must be collected to determine the effectiveness of the screening programme in each area.

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The introduction of tandem mass spectrometry (MSMS) into front line newborn screening brings with it a series of challenges, not least of which is determining the significance of determining whether a borderline result is normal or abnormal. Education of treating health professionals and affected families about unfamiliar disorders also pose significant challenges.

Building on experience from earlier newborn screening programmes, such as those for congenital hypothyroidism and cystic fibrosis, factors critical for programme success have been determined and distilled into 4 major principles (Fig. 1) A high quality laboratory is the essential backbone of a successful tandem mass spectrometry programme and this point cannot be emphasised too strongly.

Tandem mass spectrometry screening measures 2 main groups of analytes: amino acids and acyl carnitine species for the detection of aminoacidopathies, organic acidurias and fatty acid oxidation defects respectively. Calculation of specific amino acid and acyl carnitine ratios increases the specificity of the results generated by the testing

programme and increases confidence in the results. Our programme uses 13 acyl carnitine stable isotope and 9 amino acid internal standards, increasing the ratios that can be calculated. The optimum time for diagnosis of inborn errors of metabolism is around 48 hours of age, but diagnosis is possible (with reduced sensitivity) between 24 and 72 hours.

Current experience suggests that the diagnosis of phenylketonuria and some of the urea cycle defects (citrullinemia and argininosuccinic aciduria) is straightforward using MSMS. More problematic ones are maple syrup urine disease, homocystinuria, particularly the B12 responsive forms. In addition, larger programmes such as the Bavarian programme (personal communication – Professor A Roscher) suggests that only two-thirds of the cases of non-ketotic hyperglycinemia will be detected. Importantly, tyrosinemia type 1 will not be detected by neonatal testing unless a second tier method to detect succinyl acetone is used, although the other forms of tyrosinemia are clearly evident.

¹ Department of Genetic Medicine, Children's Youth and Women's Health Service, North Adelaide, Australia
Address for correspondence: Dr Janice Fletcher, Biochemical and Community Genetics SA Pathology (Women's and Children's Hospital), 72 King William Road, North Adelaide Australia 5006.
Email: Janice.fletcher@adelaide.edu.au

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- Laboratory excellence makes the life of the clinician easier
 - A good data management system is critical
 - Data analysis software is essential
 - Referral to an external expert laboratory for samples with results of unknown/uncertain significance
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Fig. 1. Principles for a successful programme.

Once elevated metabolites are recognised in a screening sample, the disorder must be confirmed by formal testing. In general, the infant should be recalled as a matter of urgency. Suspected urea cycle defects and maple syrup urine disease are relative emergencies because of the risk of cerebral oedema with metabolic decompensation. We have found that how that first information is given to the family influences future interactions and recommend great care be taken with delivering the results. The process of notification of abnormal screening results to the family will vary according to local practice: in some situations, contact is by a counsellor or physician attached to the newborn screening service. In others, an intermediary such as a paediatrician, midwife or general practitioner delivers the news. In the latter situation, we have found it to be critically important to provide written information on the disorder, as well as the results, to the person who will be contacting the family. As they are unlikely to have dealt with this disorder previously, this information should be faxed immediately to provide a factual basis for the discussion. In 21st century, most parents in Australia present for review having already gained information from the internet.

For aminoacidopathies, blood and urine should be collected for formal amino acid analysis. Other tests may be indicated, depending on the abnormality, e.g. plasma total homocysteine for homocystinuria, plasma liver function tests, coagulation profile and urine succinyl acetone for elevated tyrosine, plasma ammonium and urine orotic acid for urea cycle defects.

Confirmatory testing for organic acidurias and fatty oxidation defect will depend on the disorder suspected, but, in general, urine organic acids, plasma carnitine and repeat blood spot testing are performed. Caution must be taken in the interpretation of acyl carnitine profiles outside the optimum screening window as these can be normal, even in affected infants, in the long chain fatty acid oxidation defects.

Even once the disorder is confirmed, the significance of the diagnosis for that family may not be known. Mild cases of conditions such as very long chain acyl CoA dehydrogenase (vLCAD) deficiency and isovaleric acidemia are increasingly being recognised by newborn screening. The significance of conditions such as short chain acyl CoA dehydrogenase (SCAD) deficiency, short branched chain acyl CoA dehydrogenase deficiency and 3

methyl-crotonyl Co A dehydrogenase deficiency are currently being hotly debated among the metabolic community, with the majority opinion in 2008 that these are benign conditions.

Counselling in such situations must be skilled, to ensure that parents are informed, but not unduly alarmed, and understand the reasons the diagnosis has been raised as a possibility, the limitations of current knowledge and the management plan for future intercurrent infections. It is helpful to discuss ambiguous situations and results with a colleague or supervisor.

Parents should be provided with written information, preferably in their local language. For fatty acid oxidation defects, definition of safe fasting times, description of the signs and symptoms that should raise concern and a written, detailed, management plan for sick days is mandatory. We have written fact sheets for the more commonly seen disorders, such as MCAD deficiency.¹ Information available on the internet, even from parent support group sites, is of variable quality and may be unduly technical or alarming. If available for a particular topic, the information provided by GeneClinics (www.geneclinics.org) stands out by being comprehensive and well written.

Treatment should be supervised by an expert in the area of inborn errors of metabolism and begun as early as possible. The offending toxin should be removed from the diet. In general, if the infant is metabolically unstable or the disorder is significant, protein is excluded from the diet until the target is reached, e.g. phenylalanine below 600 $\mu\text{mol/L}$ or ammonia is normal. Vitamin therapies may be indicated. Calorie supplementation is critical to prevent or reverse catabolism. Support of vulnerable or damaged organs may be required.

Laboratory experience reduces “noise” in the screening programme, as does participation in international collaborative efforts such as the US-based Region 4 Genetics Laboratory collaborative quality improvement project.

Above all, outcomes must be audited to determine the effectiveness of the screening programme in your local setting.

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