Sheffield Children's NHS
NHS Foundation Trust

DEPARTMENT OF CLINICAL CHEMISTRY

METABOLIC DISEASE NEWSLETTER

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Editorial

2008 has been a record year for diagnoses and as we begin to plan the expansion of newborn screening to include an additional five disorders (see later abstract) it is a good time to take stock of the IMD services in East Midlands and South Yorkshire. Metabolic dietetic support in Sheffield, Nottingham and Leicester are approximately equivalent and widely acknowledged to be under-resourced. Metabolic physician cover for both adults and children, while strong in Sheffield, remains single-handed and as the recent report "Metabolic Pathways" suggests needs to be strengthened and co-ordinated across East Midlands to provide access to expert advice and continuity of care. Metabolic nursing support also needs a fresh appraisal across the Region. Fortunately, the commissioners are committed to a thorough evaluation and we have begun to consider some of these issues in a recent joint meeting of Sheffield, Nottingham and Leicester organised by the East Midlands specialist-commissioning group. This work will continue throughout the spring.

In addition to this regional initiative, the national preparation for inclusion of IMD's in the Medical specialist definition set continues and is now in its third draft. Once finalised it should help enhance the priority of IMD's for specialist commissioners and may lay the foundation for a dedicated IMD tariff which should help the business case when planning the delivery of care for these important conditions.

Awareness of inherited metabolic disorders remains a pressing clinical priority and the RCPCH is leading an initiative to audit the take up of the evidence based "reduced consciousness guidelines" which were published in 2005 and include important recommendations on testing at the time of presentation which will avoid important diagnoses being overlooked or delayed. The guidelines originally drawn together by the Paediatric Accident and Emergency Research Group led by Richard Bowker from Nottingham. Copies of this guideline are available on the RCPCH website:
http://www.rcpch.ac.uk/Research/Clinical-Audit/Reduced-Consciousness-National-Audit
Within the Region we are grateful for the support offered by Orphan UK to fund and help organise the 6th Trent Metabolic Study day, an annual educational day to review hot topics within inherited metabolic disease. We were particularly fortunate this year to have Jean-Marie Saudubray as a guest speaker. Jean-Marie is a world famous metabolic physician who practiced for many years at the Hopital Necker in Paris and has recently retired. He is a captivating speaker with a huge experience of treating neonates and children with inherited metabolic disorders and his talk was characteristically absorbing.

Abstracts from the day which was held at the Source in Sheffield on 20th November, are included in this newsletter. The meeting was well attended with over 150 delegates and another event is planned for next year.

We have continued to expand our diagnostic service with the establishment of catalase staining & *PEX1* mutation analysis for peroxisomal disorders. For the

year ahead we are anticipating establishing complementation analysis with catalase staining & extension of the *PEX* gene mutation service to include *PEX*6, 12 & 26 through collaboration with our molecular genetics service. We are also involved in a successful bid for NCS funding for the Ehlers-Danlos service. Dr Ann Dalton who heads our regional Molecular Genetics Service secured the NCS bid & the molecular genetics service now offers full mutation analysis for Ehlers-Danlos, osteogenesis imperfecta & several other genes involved in collagen regulation. It is envisaged that we will establish the biochemical service to support these collagen disorders during the forthcoming year.

Abstracts

Extended Screening: what we could achieve

Dr J R Bonham, Laboratory Director of Newborn Screening, Sheffield Children's (NHS) Foundation Trust, Sheffield, S10 2TH

Whole population screening is not a diagnostic service nor does it provide confirmatory results, it is simply a means of identifying those individuals at greater risk of having a disorder compared with those at a lower risk. Because we are approaching families that have not directly asked for help this gives us a particular burden of responsibility. This talk examines the lessons that we can learn from screening successes such as "phenylketonuria" and screening failures such as "neuroblastoma".

The potential of gateway technologies such as MSMS offer great potential to extend newborn screening to encompass a huge number of rare conditions, this can result in significant benefit to a small number of families and their children and this potential has been taken up variably throughout Europe and North America. We will discuss the plans in the United Kingdom to design a two-year research project to increase the number of conditions screened in a safe way by identifying important disorders effectively without significant dysbenefit to the wider population. The dilemma posed by the ethical issues surrounding consent and the proposed timetable for the study will be presented. It is hoped that screening for five key conditions, glutaric aciduria type 1, isovaleric acidaemia, maple syrup urine disease, homocystinuria, long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency will be included in a multi-centre study due to start in 2009/2010.

A Clinical approach to Inherited Metabolic Disorders: An overview[1]

Professor J.M. Saudubray, Hôpital Necker Enfants-Malades, Paris, France

Based mainly upon personal experience over 40 years, Professor Saudubray presented an overview of clinical clues to the diagnosis of inborn errors of metabolism in the neonate [2,3].

Inborn errors of metabolism (IEM) are individually rare, but collectively numerous. The recent application of tandem mass spectrometry (tandem MS) to newborn screening and prenatal diagnosis has enabled presymptomatic diagnosis for some IEM. However, for most, neonatal screening tests are either too slow, expensive or unreliable and, as a consequence, a simple method of clinical screening is mandatory before initiating sophisticated biochemical investigations. The clinical diagnosis of IEM relies upon a limited number of principles:

- To consider IEM in parallel with other more common conditions; for example, sepsis or anoxic-ischemic encephalopathy in neonates, and intoxication, encephalitis and brain tumours in older patients.
- To be aware of symptoms that persist and remain unexplained after the initial treatment and the usual investigations have been performed.
- To suspect that any neonatal death may possibly be due to an IEM, particularly those that have been attributed to sepsis.
- To carefully review all autopsy findings.
- Not to confuse a symptom (such as peripheral neuropathy, retinitis pigmentosa, cardiomyopathy, etc.) or a syndrome (such as Reye syndrome, Leigh syndrome, sudden infant death, etc.) with aetiology.
- To remember that an IEM can present at any age, from foetal life to old age.
- To know that although most genetic metabolic errors are hereditary and transmitted as recessive disorders, the majority of individual cases appear sporadic because of the small size of sib ships in developed countries.
- To initially consider inborn errors which are amenable to treatment (mainly those that cause intoxication)?
- In the acute, emergency situation, to undertake only those few investigations that are able to diagnose treatable IEM.
- To obtain help from specialised centres.

Do not miss a treatable disorder
First take care of the patient (emergency treatment) and then the family (genetic counselling)

1. Classification

From a pathophysiological perspective, metabolic disorders can be divided into the following three diagnostically useful groups.

Group 1: Disorders which give rise to intoxication. This group includes inborn errors of intermediary metabolism that lead to an acute or progressive intoxication from the accumulation of toxic compounds proximal to the metabolic block. In this group are the inborn errors of amino acid catabolism (phenylketonuria, maple syrup urine disease, homocystinuria, tyrosinaemia etc.), most organic acidurias (methylmalonic, propionic, isovaleric etc.), congenital urea cycle defects, sugar intolerances (galactosaemia, hereditary fructose intolerance), metal intoxication (Wilson, Menkes, haemochromatosis), and porphyrias. All the conditions in this group share clinical similarities: they do not interfere with the embryo-foetal development and they present with a symptom-free interval and clinical signs of "intoxication", which may be acute (vomiting, coma, liver failure, thromboembolic complications etc.) or chronic (failure to thrive, developmental delay, ectopia lentis, cardiomyopathy etc.). Circumstances that can provoke acute metabolic attacks include catabolism, fever, intercurrent illness and food intake. Clinical expression is often both late in onset and intermittent. The diagnosis is straightforward and most commonly relies on plasma and urine amino acid, organic acid and acylcarnitine chromatography. Most of these disorders are treatable and require the emergency removal of the toxin by special diets, extra-corporeal procedures, or "cleansing" drugs (carnitine, sodium benzoate, penicillamine, etc.).
Although the pathophysiology is somewhat different the inborn errors of neurotransmitter synthesis and catabolism (monoamines, GABA and glycine) and the inborn errors of amino acid synthesis (serine, glutamine, and proline / ornithine) can also be included in this group since they share many characteristics: they are inborn errors of intermediary metabolism, their diagnosis relies on plasma, urine, and CSF investigations (amino acid, organic acid analyses, etc.), and some are amenable to treatment even when the disorder starts in utero, for example 3-phosphoglycerate dehydrogenase deficiency [4].

Group 2: Disorders involving energy metabolism. These consist of inborn errors of intermediary metabolism with symptoms due at least partly to a deficiency in energy production or utilization within liver, myocardium, muscle, brain or other tissues. This group can be divided into mitochondrial and cytoplasmic energy defects. Mitochondrial defects are the most severe and are generally untreatable. They encompass the congenital lactic acidaemias (defects of pyruvate transporter, pyruvate carboxylase, pyruvate dehydrogenase, and the Krebs cycle), mitochondrial respiratory chain disorders and the fatty acid oxidation and ketone body defects. Only the latter are partly treatable. Cytoplasmic energy defects are generally less severe. They include disorders of glycolysis, glycogen metabolism and gluconeogenesis, hyperinsulinism (all treatable disorders), the more recently described disorders of creatine metabolism (partly treatable), and the new inborn errors of the pentose phosphate pathways (untreatable). Common symptoms in this group include hypoglycaemia, hyperlactic acidaemia, hepatomegaly, severe generalized hypotonia, myopathy, cardiomyopathy, failure to thrive, cardiac failure, circulatory collapse, sudden unexpected death in infancy, and brain involvement. Some of the mitochondrial disorders and pentose phosphate pathway defects can interfere with the embryo-foetal

development and give rise to dysmorphism, dysplasia and malformations [5]. Diagnosis is difficult and relies on function tests, enzymatic analyses requiring biopsies or cell culture, and on molecular analyses.

Group3: Disorders involving complex molecules. This group involves cellular organelles and includes diseases that disturb the synthesis or the catabolism of complex molecules. Symptoms are permanent, progressive, independent of intercurrent events and unrelated to food intake. All lysosomal storage disorders, peroxisomal disorders, disorders of intracellular trafficking and processing such as alpha-1-antitrypsin, carbohydrate deficient glycoprotein (CDG) syndrome, and inborn errors of cholesterol synthesis belong to this group. Almost none are treatable acutely; however enzyme replacement therapy is now available for several lysosomal disorders.

1. SaudubrayJM et al. A Clinical Approach to Inherited Metabolic Disorders. In: Fernandes J, Saudubray JM, Van den Berghe G, Walter J (eds) Inborn Metabolic Diseases : Diagnosis and Treatment, 4th Edition, Springer-Verlag, Heidelberg, 2006, .

2. Saudubray JM. Inborn Errors of Metabolism (2002). Seminars in Neonatology 7: issue 1 (1 volume).

3. Saudubray JM, Nassogne MC, de Lonlay P, Touati G (2002) Clinical approach to inherited metabolic disorders in neonates: an overview. Semin Neonatol 7: 3-15.

4. Klomp LW, van Oppen AC et al (2004) Prenatal and early postnatal treatment in 3-phosphoglycerate-dehydrogenase deficiency. Lancet 364: 2221-2222.

5. Van Spronsen FJ, Smit GPA, Erwich JJHM (2005) Inherited metabolic diseases and pregnancy. BJOG: an International Journal of Obstetrics and Gynaecology 112: 2-11.

Acute Neonatal Metabolic Disease: Biochemical Investigations

Professor Rodney Pollitt, Sheffield Children's (NHS) Foundation Trust, Sheffield, S10 2TH

Laboratory investigations of patients suspected of having an inherited metabolic disease fall into two main categories:

1) Specialised investigations guided by clinical pointers such as dysmorphism, specific neurological symptoms, or other syndromic features. Often such investigations are available in only a few specialised centres, those for lysosomal storage disorders, peroxisomal biogenesis defects, or carbohydrate-deficient glycoprotein syndromes being examples. It may take some time to characterise such defects fully but as many are essentially untreatable; the main value of such detailed investigations lies in the potential for antenatal diagnosis in future pregnancies.

2) General investigations, often requested under the heading of "metabolic screen", aimed at uncovering a variety of disorders, many presenting with rather non-specific acute symptoms. These investigations will usually consist of a variety of simple preliminary tests, probably carried out at local level, followed by more complex analyses, such as amino-acids, organic acids and acylcarnitines, which require special instrumentation and considerable experience in interpretation. Many of the disorders affecting these areas of metabolism require rapid treatment for a good outcome and timeliness of investigation is a critical factor in choosing which technologies to use.

The inherent biological limitations of the "metabolic screen" approach are fairly well-understood. External quality assurance schemes have revealed shortcomings also in laboratory performance, both in analytical procedures and in interpretation of abnormal results. Good communications between laboratory investigators and referring clinicians are essential for an optimal service.

Acute Neonatal Metabolic Diseases - Overview of Treatment

Dr Mark Sharrard, Consultant in Paediatric Metabolic Disease, Sheffield Children's (NHS) Foundation Trust, Sheffield, S10 2TH

Acutely presenting inherited metabolic disease (IMD) affecting the newborn infant presents in certain clinical patterns. Infants become unwell with dehydration and electrolyte imbalance and will require rehydration and ventilatory support. Cerebral oedema can be treated with standard therapy such as ventilation and mannitol. Infants may also be septic and infection may need to be treated simultaneously.

Acute encephalopathy may develop after a variable period in a full term infant who appeared normal at birth. Symptoms may develop as catabolism proceeds and toxins accumulate. As soon as an IMD is suspected, milk feeds should be stopped and an infusion of 10% dextrose with appropriate electrolytes commenced at normal maintenance rates. Insulin may also be used to promote anabolism if there is hyperglycaemia (glucose >10mmol/L). In cases of severe acidosis, sodium bicarbonate may be used cautiously, with care to avoid sodium overload. Hyperammonaemia with alkalosis or minimal acidosis suggests a urea cycle disorder (UCD). Residual urea cycle activity is stimulated with intravenous arginine and alternative pathways of ammonia excretion activated with intravenous sodium benzoate and sodium phenylbutyrate. If NAGS or CPS deficiency is suspected, carbamyl glutamate should be given. If the initial ammonia is >300μmol/L or fails to respond to intravenous therapy, extracorporeal detoxification (ED) should be used. Metabolic acidosis with an expanded anion gap is suggestive of an organic acidaemia (OA), or fat oxidation disorder (FAOD) if there is hypoglycaemia and no ketosis. Hyperammonaemia can be treated with alternative pathway activation, and carbamyl glutamate used to stimulate the urea cycle. Carnitine is given to prevent depletion and assist detoxification. ED should be used if there is failure of acidosis or hyperammonaemia to respond to intravenous therapy. If there is only moderate acidosis and hyperammonaemia with a urinary odour of maple syrup, the infant may have maple syrup urine disease and will require general supportive measures and ED to remove leucine. In the case of an undiagnosed organic acidaemia, vitamin B12 and biotin should be given in case of vitamin responsiveness. Lactic acidosis and MSUD may be treated with a trial of thiamine. In FAODs not clinically responding to glucose therapy, provision of ketones as 3-hydroxybutyrate may be effective.

Once metabolic stability is restored, UCDs and OAs will require treatment with a protein restricted diet, with adequate calories and micronutrients. Protein intake should be restarted as soon as possible to prevent catabolism. Long chain FAODs will require a low fat diet supplemented with medium chain triglycerides, vitamins and essential fatty acids.

Intractable seizures of early onset may suggest a pyridoxine, pyridoxal phosphate or folinate responsive disorder, and these vitamins should be tried sequentially in pharmacological doses. Serine deficiency disorders can be

treated with serine and glycine supplementation. Sulphite oxidase and molybdenum cofactor deficiencies, and non-ketotic hyperglycinaemia do not respond to metabolic therapies.

Hypoglycaemia may accompany many IMDs but if persistent suggests an FAOD, glycogen storage disease type I ((GSD 1), fructose bisphosphatase deficiency (FBPD) or hyperinsulinism. GSD 1 and FBPD have an associated lactic acidosis and hepatomegaly which respond to 10% glucose infusion and then regular high carbohydrate feeds. A glucose administration rate of > 10mg/kg/min to maintain blood glucose >3mmol/L suggests neonatal hyperinsulinism. Initial treatment can be with diazoxide and glucagon.

Liver failure starting with conjugated hyperbilirubinaemia after exposure to milk feeds suggests galactosaemia. There may be associated *E.coli* sepsis. All lactose containing feeds including breast milk should be stopped, and liver failure treatment commenced. Hereditary fructose intolerance may present as an acidotic crisis with liver failure if the infant exposed to fructose or sucrose. Tyrosinaemia type 1 occasionally presents as liver failure in the newborn period and is treated with NTBC and a low tyrosine/phenylalanine diet.

Cardiac failure may be a consequence of mitochondrial disease or a FAOD. In the latter case, there may be response to FAOD treatment including ketones. Primary carnitine deficiency may present with cardiac failure and responds to carnitine therapy. Mitochondrial disorders may occasionally respond to ubiquinone or riboflavin and carnitine if deficient, but treatment is rarely satisfactory.

Congenital lactic acidosis may be due to pyruvate dehydrogenase (PDH) deficiency, pyruvate decarboxylase deficiency or mitochondrial respiratory chain disorders. Lactate may become more elevated with glucose administration, and intravenous infusion of 5% glucose should be given. A trial of biotin should be given in case of a biotin responsive disorder, and thiamine if PDH deficiency is suspected, or riboflavin and ubiquinone for mitochondrial disease.

Drugs for the Emergency Treatment of inborn errors of Metabolism

Gillian Hinson, Senior pharmacist, Sheffield Children's (NHS) Foundation Trust, Sheffield, S10 2TH

As you know the urgent treatment of children with inborn errors of metabolism is vitally important in improving their clinical outcome during periods of critical illness. When patients are referred to the Sheffield Children's Hospital (SCH) a box containing a number of essential drugs used in metabolic conditions is available complete with dosing guidelines.

This box is used within the hospital so that the required drugs can be easily and quickly located. The dosing guidelines which are attached to the metabolic box provide the correct doses, administration instructions and compatibility data. This readily available information enables the medical and nursing staff to quickly and safely prescribe and administer these drugs.

This box has is available on request and can be sent out by taxi to other hospitals in order to start treatment and stabilise the child prior to transfer to SCH. Unfortunately, there is invariably a delay in this process, particularly if the box is being sent a long distance from SCH.

To improve the service even more and to reduce the time to starting treatment to an absolute minimum we are proposing to make these 'metabolic boxes' available to any hospital to purchase.

The box will have all the items in it that are currently available from the SCH with the exception of the Carbaglu (Carglumic acid) tablets. The decision to stock these will be for local agreement due to the cost of the product.

Each box will have the following items:

3 x 20ml Arginine injection 210mg in 1ml
6 x 1ml Biotin injection 5mg in 1ml
20 x 5mg Biotin tablets 5mg
5 x 5ml Carnitine injection 200mg in 1ml
5 x 1ml Hydroxycobalamin injection (Vitamin B12) 1mg in 1ml
10 x 5ml Sodium Benzoate injection 200mg in 1ml
10 x 5ml Sodium Phenylbutyrate injection 200mg in 1ml

The box will be complete with expiry date and will contain all the usual prescribing and administration information.

The cost of the complete box will be approximately £270

Cases for Trent Metabolic Study Day

Camilla Reed, Principal Clinical Scientist, Sheffield Children's (NHS) Foundation Trust, Sheffield, S10 2TH

Case 1:

A baby born to consanguineous parents (1st cousins), who had one older sibling (female) 2 years old who was fit and well, started being unwell on day 5 of life and was noted to be sleepy and not feeding well. Biochemistry showed a mixed metabolic and respiratory acidosis with a raised lactate. Initial plasma ammonia was measured at 286 µmol/L. However the baby continued to deteriorate and was subsequently intubated and transferred to PICU. A repeat ammonia came back at 800 µmol/L and the ammonia peaked at 1200 µmol/L. Urgent metabolic investigations were carried out at this stage and the plasma citrulline was measured at 2006 µmol/L. Based on the full amino acid profile a diagnosis of citrullinaemia was made. This case is a simple case of a common metabolic disorder but highlights the prompt need for acting on and repeating a raised ammonia level to prevent long term clinical consequences.

Case 2:

An infant born to consanguineous parents who already had a child with MSUD was tested at birth for levels of branched chain amino acids which were found to be normal. On day 3 of life she presented with septicaemia and jaundice. A urine metabolic screen consisting of organic and amino acids was carried out. No specific disorder was identified but it was noted that she had a generalised aminoaciduria. Her urine also tested positive for reducing substances which was later confirmed as galactose by TLC. Subsequently a blood sample was tested for galactose-1-phosphate uridyl transferase which showed no activity and a diagnosis of classical galactosaemia was made. The child was started on a galactose free diet and initially had a good response. However at 4 months she was re-admitted to hospital with seizures and regression. Serum and CSF lactate were both elevated. A second urine was analysed for organic acids which now demonstrated increased excretion of 3OH-isovalerylglycine, 3-methylcrotonylglycine, methyl citrate and 3OH-isovalerate. These metabolites and the clinical presentation were suggestive of biotinidase deficiency which was confirmed by deficient enzyme activity in plasma. This case highlights the need to keep an open mind when a clinical condition does not follow the expected path and to keep looking for metabolic and non-metabolic disease in these instances.

Acknowledgements: Dr Guy Besley & Dr. John Walter, The Willink Biochemical Genetics Unit, Manchester Children's Hospital.

Dr Simon Olpin, Consultant Clinical Scientist, Sheffield Children's (NHS) Foundation Trust, Sheffield, S10 2TH

Case 3: A 3.2 kg normal baby was born at term to Pakistani parents who were first cousins. He was observed to be unresponsive, gasping, cyanosed and bradycardic at 42 h of age. Blood glucose was <0.1 mmol/L and no ketones were detected in the urine at the time of collapse. In spite of intravenous glucose and ventilatory support he suffered a respiratory arrest and subsequent loss of cardiac output. He was successfully resuscitated but a second episode of ventricular fibrillation occurred two hours later which responded to a single DC shock. Echocardiography showed no structural abnormality. Plasma glucose and electrolytes were normal at the time of his arrest. Plasma ammonia was 390 μmol/L and lactate 10 mmol/L. CK and lactate dehydrogenase were normal but urine organic acids showed a moderate dicarboxylic aciduria with some 3-hydroxydicarboxylic acids. Plasma total and free carnitines were 15 and 12 μmol/L respectively, which we would consider to be at the lower limit of the normal range for a neonate. Acylcarnitine profiling was not available at that time. However, at two months of age, total and free carnitines were 72 and 67 μmol/L respectively (corresponding normal ranges 23-60 and 15-53). A 24h ECG at 3 weeks of age was normal. He made good progress following these early life threatening episodes and was discharged home with a working diagnosis of a long-chain fatty acid oxidation defect, on frequent, low fat, carbohydrate rich feeds with strict avoidance of fasting. Subsequently a diagnosis of carnitine palmitoyl transferase type 1 was made on cultured fibroblasts.

He was well until 5 months of age when he developed rotavirus gastroenteritis, tender hepatomegaly and raised transaminases, but remained normoglycaemic. He developed persistently low serum bicarbonate and elevated chloride consistent with renal tubular acidosis. Plasma bicarbonate ranged between 7-13 mmol/L with an anion gap of ~20, although urine pH was not measured. Tubular maximum reabsorption of phosphate/glomerular filtration rate (TmP/GFR) was 0.93 (reference range 1.15 - 2.6), thus indicating significantly impaired tubular function with respect to active transport of phosphate. Dietary medium-chain triglyceride (MCT; Monogen) was commenced, with oral bicarbonate supplementation. The renal tubular acidosis resolved within 10 days. He is now thriving on a low fat diet supplemented with MCT. An emergency feed regime is available in the event of intercurrent illness. This case serves to highlight the importance of an accurate early diagnosis. The transient cardiac arrhythmias seen in neonatal CPTI deficient infants are thought to be due to the expression of remaining residual foetal isoform of CPTIA in cardiac tissue. This isoform is generally thought to be completely replaced by the normal muscle isoform of CPTI during the neonatal period. The renal tubular epithelial cells have a high requirement for ATP with fatty acids as the preferred substrate. Renal tubular acidosis is a recognised complication of CPTI deficiency but responds to medium chain triglyceride supplementation.

Case 4: A male infant, born to consanguineous Asian parents developed vomiting, diarrhoea and mild transient hyperammonaemia (180 to 220 μmol/l) at thirteen days of age. He failed to thrive on a combination of breast milk and

standard infant formula and required blood transfusions for a severe anaemia. Haemoglobin was 8.8g/dl, a blood film showed spherocytes, fragmented cells and polychromasia. Plasma glutamine was elevated; ornithine and citrulline were low but urine orotic acid was slightly raised at 17 μmol/mmol creatinine. However, a repeat blood ammonia four hours after starting intravenous dextrose was normal and remained normal over the next four days while standard infant formula feeds were reintroduced. The main clinical problem was persistent anaemia necessitating packed cell blood transfusions over the ensuing four weeks. Bone marrow examination showed an excess of binucleate erythroblasts and occasional trinucleate forms suggestive of a congenital dyserythroblastic anaemia. During this period the infant continued to vomit intermittently and weight gain remained poor. At age six weeks he became encephalopathic within a few hours of completing a blood transfusion. His blood ammonia was 812 μmol/l; he was urgently treated with intravenous sodium benzoate and arginine while protein feeds were discontinued. Blood ammonia fell to normal within 24 hours of treatment but the patient remained irritable with abnormal cycling movements for three days. Subsequently he was maintained on a low protein diet (approximately 1.5g/kg/24 hours) with oral arginine supplements and sodium benzoate medication. Plasma amino acids at age six weeks showed a low ornithine of 19 mmol/L with no detectable citrulline but high glutamine. By seven weeks there was a marked elevation of plasma ornithine and reduced glutamine. Urine orotic acid was also markedly increased and homocitrulline was detected in urine, however this can be a normal constituent for infants on milk formula feeds. Investigation of [^{14} C]-ornithine incorporation into fibroblast cell protein was markedly deficient consistent with either the ornithine transporter defect (hyperornithineaemia-hyperammonaemia-homocitrullinuria syndrome) or ornithine aminotransferase (OAT) deficiency. Subsequent studies showed a severe deficiency of OAT activity, indicating this to be the underlying defect. Mutation analysis of the OAT gene on RNA prepared from cultured skin fibroblasts revealed that this patient is homozygous for the 1192C->T (R398ter) mutation in exon 11. Once the diagnosis of OAT deficiency was established, arginine supplements were discontinued and he was started on a low arginine diet. He has had no further episodes of hyperammonaemia. At one year he was healthy, had normal growth (weight 10-50th centile, height 3rd centile) and has achieved developmental milestones appropriate for his age. Ophthalmic examination was normal. He was no longer transfusion dependent and the bone marrow now had a normal appearance. The patient is now 6 years old and has remained in good health although he continues to be anaemic with haemoglobin values of 8.2 – 10.4g/dl.

OAT is a reversible enzyme which normally functions to degrade ornithine. However in the neonate arginine is in short supply & OAT serves to supply ornithine for the urea cycle. In OAT deficiency low ornithine availability in the neonatal period impairs the urea cycle & leads to hyperammonaemia. Outside this early period plasma ornithine rises & untreated patients develop frank hyperornithinaemia which leads to “gyrate atrophy”.

Diagnosis List	
2008	
4-Hydoxy-butyric aciduria	1
Biotinidase deficiency	1
Carbamylphosphate synthase 1 CPS1	1
CDPX2 [Conradi-Happle-Hunnermann]	2
Cerebrotendinous Xanthomatosis	5
CPT 1	1
CPT 2	4
CPT2 or CATR	1
Cystinuria	2
Cystinuria (carrier)	3
D-2-hydroxyglutaric aciduria	2
Fumarase Deficiency	2
GA 1	4
GA 2 -severe	2
Galactosaemia	1
Glutathione synthetase deficiency	2
Hypophosphatasia	1
Isovaleric acidaemia	1
L-2-hydroxyglutaric aciduria	3
Long chain 3-hydroxacyl-CoA dehydrogenase LCHAD	4
Medium chain acyl-CoA dehydrogenase MCAD	12
MCAD (heterozygote) plus "mild" MADD	1
Mucopolysaccharidosis type 1	1
Holocarboxylase synthase deficiency	1
Neuroblastoma	1
Non-ketotic hyperglycinaemia	1
N-acetylglutamate synthase NAGS	1
Pyruvate dehydrogenase PDH	1
Peroxisomal biogenesis disorder [?RCDP]	1
Peroxisomal defect [Beta oxidation defect]	1
Phenylketonuria	2
Pyridoxine dependent epilepsy	2
Renal Fanconi Syndrome	1
Mitochondrial Repiratory Chain defect	8
Sulphite Oxidase deficiency	1
Trimethylaminuria	83
Very long chain acyl-CoA dehydrogenaase VLCAD	2
X-linked Adrenoleukodystrophy ALD	4
X-linked Adrenoleukodystrophy [carrier]	1
Zellweger	5
TOTAL	**173**

Newborn Screening Diagnoses: January – December 2008

Screening covers South Yorkshire, South Humberside and the full East Midlands SHA Region *

Total babies screened 75,130

Cases detected by screening for Phenylketonuria (increased phenylalanine)

PKU	14
Hyperphenylalaninaemia	1
Galactosaemia	1

Cases detected by screening for MCAD deficiency (increased octanoylcarnitine)

MCAD deficiency	11
Homozygous c.985 A>G	6
Compound heterozygotes	5
Unaffected carrier c.985 A>G	2

* For information or details related to screening please contact Melanie Downing, Lead Scientist Newborn Screening
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