Institution: University College London

Unit of Assessment: 1 – Clinical Medicine

Title of case study: Inborn errors of metabolism: diagnosis and treatment

1. Summary of the impact

Investigators at UCL have developed new diagnostic tests, new treatments and new methods for monitoring treatment of inborn errors of metabolism. Certain of these tests are now used to screen all newborns in the UK, all infants with liver disease and all infants with drug-resistant epilepsy. This is improving outcome for >120 UK children per year. For untreatable disorders, prenatal tests prevent the birth of a second affected child in the family.

2. Underpinning research (indicative maximum 500 words)

Inborn errors of metabolism are genetic disorders characterised by a defective protein that disturbs an important metabolic pathway. Inborn errors of metabolism are individually rare but collectively common diseases, and can cause a very wide range of symptoms and signs from liver disease to convulsions to movement disorders to loss of consciousness on fasting.

MCADD

Medium-chain acyl-CoA dehydrogenase deficiency (MCADD) is a rare genetic condition in which a person has problems breaking down fatty acids for energy. It affects around 1 in 10,000 babies born in the UK each year, and is life-threatening if not discovered early, as any drop in an affected baby's blood sugar levels can result in severe illness or death. In 1998, working with Micromass UK Ltd, we showed that electrospray ionisation tandem mass spectrometry could be used to measure octanoylcarnitine in blood spots thus providing the basis for an automatable method for screening for MCADD **[1]**. We showed that once MCADD had been diagnosed and appropriately managed, the prognosis was excellent (whereas in undiagnosed patients the mortality was 20-25% and a further 20% of children were left disabled) **[2]**.

Fabry disease

Fabry disease is a rare lysosomal storage disorder, affecting around 1 in 58,000 individuals. The condition has serious complications including severe neuropathic pain, renal failure, cardiomyopathy and coronary artery disease, and strokes. Patients often die prematurely as a result of these complications. In 2002 we published a new method for determination of ceramide trihexoside (CTH) in plasma and urine of patients with Fabry disease **[3]**. Such measurements have proved useful in monitoring enzyme replacement therapy. This method is now the gold standard test for the screening and monitoring of enzyme replacement throughout the UK and worldwide.

Movement disorders

We were the first to show, in 1993, that parkinsonism in infants can be caused by a disorder affecting the synthesis of dopamine (aromatic amino acid decarboxylase [AADC] deficiency); some affected patients have shown a good response to dopamine agonists and monoamine oxidase inhibitors, and new treatments have been developed by ourselves and others which build on our early work **[4]**. We have also shown that dystonia in older children can be caused by a disorder leading to the build-up of manganese in the brain **[5]**. This disorder can be effectively treated with a manganese chelator and iron supplementation. We developed tests for dopamine and serotonin metabolites in cerebrospinal fluid (CSF) (for diagnosis of AADC) and we found the gene responsible for the manganese disorder, thereby providing a genetic test. Overall, this work has led to the development of useful diagnostic tests and new treatments for children and adults with movement disorders.

Epilepsy

In 2005 we identified the genetic defect responsible for a severe seizure disorder in infancy which

we had previously shown could be treated effectively with pyridoxal phosphate (the active form of vitamin B6). In 2006 we showed that severe seizures in the newborn that respond to treatment with pyridoxine (another form of vitamin B6) could be due to another genetic defect (antiquitin deficiency) **[6]**.

Progressive liver disease

We have shown that liver disease in infancy and neurological disease in older children and adults can be caused by disorders of bile acid synthesis and these disorders can respond extremely well to bile acid replacement therapy. Without treatment children can progress to cirrhosis and liver failure **[7]**.

3. References to the research (indicative maximum of six references)

[1] Clayton PT, Doig M, Ghafari S, Meaney C, Taylor C, Leonard JV, Morris M, Johnson AW. Screening for medium chain acyl-CoA dehydrogenase deficiency using electrospray ionisation tandem mass spectrometry. Arch Dis Child. 1998 Aug;79(2):109-15. http://dx.doi.org/10.1136/adc.79.2.109

[2] Wilson CJ, Champion MP, Collins JE, Clayton PT, Leonard JV. Outcome of medium chain acyl-CoA dehydrogenase deficiency after diagnosis. Arch Dis Child. 1999 May;80(5):459-62. http://dx.doi.org/10.1136/adc.80.5.459

[3] Mills K, Johnson A, Winchester B. Synthesis of novel internal standards for the quantitative determination of plasma ceramide trihexoside in Fabry disease by tandem mass spectrometry. FEBS Lett. 2002 Mar 27;515(1-3):171-6. http://dx.doi.org/10.1016/S0014-5793(02)02491-2

[4] Pons R, Ford B, Chiriboga CA, Clayton PT, Hinton V, Hyland K, Sharma R, De Vivo DC. Aromatic L-amino acid decarboxylase deficiency: clinical features, treatment, and prognosis. Neurology. 2004 Apr 13;62(7):1058-65. http://dx.doi.org/10.1212/WNL.62.7.1058

[5] Tuschl K, Mills PB, Parsons H, Malone M, Fowler D, Bitner-Glindzicz M, Clayton PT. Hepatic cirrhosis, dystonia, polycythaemia and hypermanganesaemia--a new metabolic disorder. J Inherit Metab Dis. 2008 Apr;31(2):151-63. http://dx.doi.org/10.1007/s10545-008-0813-1

[6] Mills PB, Struys E, Jakobs C, Plecko B, Baxter P, Baumgartner M, Willemsen MA, Omran H, Tacke U, Uhlenberg B, Weschke B, Clayton PT. Mutations in antiquitin in individuals with pyridoxine-dependent seizures. Nat Med. 2006 Mar;12(3):307-9 http://dx.doi.org/10.1038/nm1366

[7] Clayton PT. Disorders of bile acid synthesis J Inherit Metab Dis. 2011 Jun;34(3):59 3-604. http://dx.doi.org/10.1007/s10545-010-9259-3

4. Details of the impact (indicative maximum 750 words)

MCADD

Our demonstration of an automatable method for MCADD screening and the resulting benefits to patients contributed to a decision to undertake a pilot study of MCADD screening (UKCSNS-MCADD) which was co-ordinated by the MRC Centre of Epidemiology for Child Health at the UCL Institute of Child Health, London **[a]**. This pilot study showed good results, and so MCADD screening was adopted in England in 2009 and Wales in 2012 using our methods **[b]**. Since screening began, we can estimate (based on epidemiology in ref 2 above) that around 60 lives have been saved and around 60 cases of long-term disability prevented. One such example was recently highlighted on the Great Ormond Street Hospital website – the parents of a child identified by screening could be given specialist dietary advice and training on what to do in an emergency **[c]**.

Fabry disease

Our CTH method has been adapted for screening programmes. For example, screening of 172,000 newborns in Taiwan identified 89 infants with low activity of the Fabry enzyme; these infants were further assessed using our urine CTH method **[d]**. Enzyme replacement therapy (ERT) has been approved by for the treatment of Fabry disease, and early treatment can help to avoid complications. As well as contributing to early diagnosis, our tests provide early evidence of the success of ERT by falling levels of CTH in the urine. We are commissioned to test urine samples from patients receiving enzyme replacement therapy by one of the companies producing the enzyme (Genzyme). Between 2008 and 2013 we analysed 760 samples per year. Income from the CTH tests (£37,000 p.a.) and other tests undertaken in our laboratories (£41,000 p.a.) contributes to maintenance of equipment and funds further method development **[e]**.

Movement disorders

Our diagnostic tests and new treatments for movement disorders are now in use in clinical practice. The treatment we devised for genetically determined manganese build-up dramatically alleviated symptoms of parkinsonism or dystonia in four sufferers during the period 2008-13 **[f]**. This work was featured on the website of the European Parkinson's Disease Association **[g]**.

As a result of our work on Aromatic Amino Acid Decarboxylase Deficiency (AADC), diagnostic tests are now available **[h]**. Without our research all the families on this website would have no diagnosis for their child's extremely debilitating disorder. Now those that have not responded to drugs are likely to be able to have gene therapy in a joint UK/US venture. Our work on diagnosis of AADC is featured on the AADC Research Trust website **[i]**.

Epilepsy

Our research on epilepsy has resulted in new diagnostic tests and better treatment for infants and children now in use. We perform diagnostic tests on 230 urine samples and 46 DNA samples per year, sent to us from paediatricians looking after infants and children with severe epilepsy around the country. Between 2008 and 2013, we identified the genetic biochemical defect in 35 children (14 with pyridoxine 5'-phosphate oxidase (PNPO) deficiency; 21 with antiquitin deficiency). These are potentially fatal disorders. They respond poorly to antiepileptic drugs but respond very well to high doses of vitamin B6 as pyridoxine or pyridoxal phosphate. Our diagnostic test thus enables more successful treatment to be given. **[e]**

Our research was quoted in a recent guideline on treatment of neonatal seizures **[j]**. Referencing [5] above, along with another publication from our group, the guidelines recommend: "*Most cases of pyridoxine-dependent epilepsy are due to alpha-aminoadipic semialdehyde dehydrogenase (also known as antiquitin, or ATQ) deficiency, an autosomal recessive inborn error of metabolism caused by defects in the ALDH7A1 gene that lead to accumulation of alpha-AASA. Mutation analysis of the ALDH7A1 gene is recommended in patients with abnormal biochemical screening and/or clear evidence of pyridoxine or folinic acid responsiveness*."

Progressive liver disease

Our research on progressive liver disease means that children can now be given bile acid replacement therapy for an increasing number of bile acid synthesis disorders, preventing death from liver disease or the need for a liver transplant **[k]**. We analyse samples from patients presenting with cholestatic liver disease in the UK and overseas (280 samples, 4 treatable positives per year). For the period 2008-13, this equates to 24 lives saved / transplants avoided. In 2011, a bile acid preparation, Orphacol, was licensed by the European Medicines Agency for the treatment of inborn errors in primary bile acid synthesis. In the submission, they state that: "The literature provided by the applicant showed that, where available to investigators, the clinical use of cholic acid has been documented since at least the mid-1990s through the work primarily conducted by the Jacquemin, Clayton and Setchell groups". The document references 10 of our

papers **[l]**.

5. Sources to corroborate the impact (indicative maximum of 10 references)

[a] Oerton J, Khalid JM, Besley G et al. 2011. Newborn screening for medium chain acyl-CoA dehydrogenase deficiency in England: prevalence, predictive value and test validity based on 1.5 million screened babies. Journal of Medical Screening 18:173-181 http://dx.doi.org/10.1258/jms.2011.011086

[b] Details of MCADD screening: http://newbornbloodspot.screening.nhs.uk/mcadd and see also laboratory guide referencing our publication: http://newbornbloodspot.screening.nhs.uk/getdata.php?id=11526

[c] http://www.gosh.org/mgf/events-and-appeals/appeals/bringing-research-to-life/impact/children-weve-helped-through-our-research/harry

[d] Chien YH, Olivova P, Zhang XK, Chiang SC, Lee NC, Keutzer J, Hwu WL. Elevation of urinary globotriaosylceramide (GL3) in infants with Fabry disease. Mol Genet Metab. 2011 Jan;102(1):57-60. http://dx.doi.org/10.1016/j.ymgme.2010.08.023

[e] For confirmation please contact Biochemistry Research Group, UCL Institute of Child Health. Contact details provided.

[f] The following three papers (two from our group, one from elsewhere) demonstrate how this work has impacted on patients:

- Stamelou M, Tuschl K, Chong WK, Burroughs AK, Mills PB, Bhatia KP, Clayton PT. **Dystonia with brain manganese accumulation resulting from SLC30A10 mutations: a new treatable disorder**. Mov Disord. 2012 Sep 1;27(10):1317-2211 http://dx.doi.org/10.1002/mds.25138
- Tuschl K, Clayton PT, Gospe SM Jr, Gulab S, Ibrahim S, Singhi P, Aulakh R, Ribeiro RT, Barsottini OG, Zaki MS, Del Rosario ML, Dyack S, Price V, Rideout A, Gordon K, Wevers RA, Chong WK, Mills PB. **Syndrome of hepatic cirrhosis, dystonia, polycythemia, and hypermanganesemia caused by mutations in SLC30A10, a manganese transporter in man**. Am J Hum Genet. 2012 Mar 9;90(3):457-66 http://dx.doi.org/10.1016/j.ajhg.2012.01.018
- Quadri M, Federico A, Zhao T, Breedveld GJ, Battisti C, Delnooz C, Severijnen LA, Di Toro Mammarella L, Mignarri A, Monti L, Sanna A, Lu P, Punzo F, Cossu G, Willemsen R, Rasi F, Oostra BA, van de Warrenburg BP, Bonifati V. **Mutations in SLC30A10 cause parkinsonism and dystonia with hypermanganesemia, polycythemia, and chronic liver disease**. Am J Hum Genet. 2012 Mar 9;90(3):467-77 http://dx.doi.org/10.1016/j.ajhg.2012.01.017

[g] http://www.epda.eu.com/en/parkinsons/in-depth/pdsymptoms/dystonia/where-can-i-get-more-information/research-papers/?p=2

[h] http://www.aadcresearch.org/Testing-Laboratory.html

[i] http://www.aadcresearch.org/The-Tawara-Twins.html

[j] http://www.uptodate.com/contents/treatment-of-neonatal-seizures

[k] Hartley JL, Gissen P, Kelly DA. Alagille syndrome and other hereditary causes of cholestasis. Clin Liver Dis. 2013 May;17(2):279-300. http://dx.doi.org/10.1016/j.cld.2012.12.004

[l] http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/001250/WC500131542.pdf