



WELCOME TO ACBI 2006

PROCEEDINGS OF

The 29th Annual Conference

Of the Association of Clinical Biochemists In Ireland

**HILTON HOTEL, CHARLEMONT PLACE
DUBLIN 2, IRELAND**

20th - 21st October, 2006





The ACBI in Ireland and the World

The Association of Clinical Biochemists in Ireland (ACBI) is the national society for Clinical (Bio)chemistry of the Republic of Ireland. The ACBI is a member society of the International Federation of Clinical Chemistry (IFCC) and of the IFCC's "geographical" sub-groups FESCC (Forum of European Societies of Clinical Chemistry) and EC4 (European Communities Confederation of Clinical Chemistry). The ACBI is a sponsoring society of Clinical Chemistry and Laboratory Medicine (formerly European Journal of Clinical Chemistry and Clinical Biochemistry).

The Association works closely on matters of common interest with its sister organizations the Academy of Medical Laboratory Science and the Faculty of Pathology of the Royal College of Physicians of Ireland through joint committees such as the Steering Committee of the Irish External Quality Assessment Scheme (Laboratory Medicine), and the Joint Working Group on Accreditation of Irish Clinical Laboratories. The Association's website is www.acbi.ie

The Association's logo incorporates Celtic symbols of knowledge and of healing, to represent science and medicine. It comprises an abstracted image of water to represent the otherworld well of wisdom, and the spring of healing, and also the cauldron of regeneration.

Also depicted are the hazels of wisdom and inspiration. It was by eating the hazel nuts, which fell into the well, that the salmon of knowledge acquired its wisdom.

The elements of the logo are grouped in threes to echo the triadic motif common in Celtic imagery.

A further characteristic is the openness to interpretation at various levels of meaning. Thus, the lower part echoes a common schematic used in biochemistry to represent molecules migrating in a matrix.





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Acknowledgements

The organizing committee for ACBI 2006 gratefully acknowledges the very generous support of the following:

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The following Major Sponsors have provided significant additional support for the Conference:

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Céad Míle Fáilte



Welcome to ACBI 2006

Cuirimid fóirchoain fáilte roimh bhail an ACBI, roimh na haíonna cáiliúla, roimh na cuairteoirí, roimh ár gcomhghleacaithe in ACBI agus roimh gach duine a fhreastalaíonn ar an gcomhdháil bhliantúil i mbliana.

We extend a warm welcome to ACBI members, to our distinguished speakers, to our guests, to our ACBI colleagues and to all who attend this conference. We hope that you will enjoy the scientific and social programmes.

As this year's conference organizing committee is based in the Children's University Hospital, Temple Street, the venue returns to Dublin and the Hilton Hotel, Charlemont. This venue was previously used for the ACBI conference in the years 1998/1999, then known as the Stakis Hotel. We hope that visitors to the City of Dublin will also find some time to extend their stay to enjoy some of the sights and entertainment that the Capital city has to offer.

Our scientific programme includes lectures on current ethical issues which are of concern in the laboratory and in the wider clinical setting. We have presentations on the application of the latest technologies, research and review papers and their relevance to the role of the clinical biochemist today.

The session for presentation of case histories provides a forum for delegates to share their findings of interest with a wide audience and allows for interactive discussion. We also have a variety of poster presentations for you to peruse.

We hope that the scientific content of the programme will enhance your knowledge and understanding and contribute to your on going professional development.

The successful organisation of this conference depends greatly on the generous support of our sponsors. We extend a special welcome to the delegates of the conference sponsors.

Finally we would like to thank the outgoing committee of ACBI 2005 who passed on their experience and advice to us and also to the members of the ACBI Council for their continuing support and encouragement.

**Deirdre Deverell (Chairperson), Maire Oakley (Conference Secretary),
Anne O Shea, Richard Walsh, Philip Mayne**

ACBI 2006 Conference Committee.



Continuing Education

The Royal Colleges

ACBI 2006 has been approved for CME by the Royal College of Physicians of Ireland (RCPI) and for CPD by the Royal College of Pathologists (RCPATH). All medical Royal Colleges in Ireland and the UK have agreed to recognise each other's approval of events.

Medical staff and clinical biochemists who have completed training and are in career grade posts and have registered for CME or CPD with one of the Royal Colleges are entitled to receive CME or CPD credits.

CME approval: Fri 20th Oct = 5 credits, Sat 21st Oct = 7 credits

CDP approval: Max 11 credits for the two day meeting

In order to receive these credits, a participant must sign the appropriate attendance register (RCPI or RCPATH) for each day or session attended and be issued with a certificate of attendance by the meeting organiser.

Academy of Medical Laboratory Science

ACBI 2006 has been approved by the Academy of Medical Laboratory Science (AMLS) for the award of CPEP points. Five CPEP points will be awarded for each half-day attended or twenty CPEP points for attendance at the full conference. In order to receive these points, an AMLS member must sign the AMLS attendance register and be issued with a certificate of attendance by the meeting organiser.

Evaluation of meeting

ACBI evaluates the quality and educational benefits of its meetings in order to maintain its tradition of high educational standards. This process also assists in the planning of future conferences. All conference participants should complete the conference evaluation form provided in the conference bag and return it to the Conference Registration Desk.

Programme



Friday 20th October 2006 (Morning)

08:30

Registration

Opening Ceremony

09:30 - 9:45

ACBI President's Address
Dr. John O'Mullane

09:45 - 10:15

Opening Lecture: Chemical Pathologist/Consultant Biochemist Services
*Mr. Tommie Martin, National Director, Office of CEO ,
Health Services Executive*

Session 1

Ethical Issues

Chairperson: Ms. Ruth O' Kelly, Coombe Women's Hospital, Dublin

10:15 - 11:00

Ethical Issues Concerning the Use of Human Biological Material.
Dr. Siobhan O Sullivan, Director, Irish Council for Bioethics

11:00 - 11:30

Tea/Coffee Break

11:30 - 12:15

Consent and Confidentiality for Clinical Procedures, Legal Implications.
Dr. Asim Sheikh B.A., L.L.M., Barrister-at-Law, UCD

12:15 - 13:00

Stem Cells, Biology and Ethics
*Professor Frank Barry, Scientific Director, Remedi, National University of
Ireland, Galway*

13:00 - 14:15

Lunch Break



Programme

Friday 20th October 2006 (Afternoon)

Session 2

'From Molecules to Migration'

Chairperson: Dr. Clodagh Loughrey, Belfast City Hospital

14:15 - 15:00

Clinical Applications of Tandem Mass Spectrometry

Mr. Richard Walsh, Children's University Hospital, Temple St., Dublin

15:00 - 15:45

Expanded Newborn Screening Programmes and Disease Definition

Professor Rodney Pollitt, Children's Hospital, Sheffield

15:45 - 16:15

Tea / Coffee Break

16:15 - 17:00

Genetics, Population History and Inherited Disorders in Ireland

Professor David Croke, Royal College of Surgeons in Ireland

17:30

ACBI Annual General Meeting (Members Only)

Friday 20th October 2006 (Evening)

19:30

Evening Entertainment

Buffet meal followed by Casino Night

Programme



Saturday 21st October 2006 (Morning)

Session 3

Neuroscience

Chairperson: Dr. Maria Fitzgibbon, University College Hospital, Galway.

9:30 - 10:15

Neuroimaging as a Diagnostic Tool

Dr. Stephanie Ryan, Children's University Hospital, Temple St., Dublin

10:15 - 11:00

Investigation of Developmental Delay

Dr. Mary King, Children's University Hospital, Temple St., Dublin

11:00 - 11:30

Tea/Coffee Break

11:30 - 12:15

Neurotransmitters: Disorders of Dopamine and Serotonin Metabolism, Analysis and Interpretation.

Dr. Simon Heales, Neurometabolic Unit, National Hospital, Queen Square, London.

12:15 - 13:00

Targeting Alzheimer's Disease: Amyloid β -protein Disruption of Synaptic Plasticity

Professor Michael Rowan, Dept of Pharmacology and Therapeutics, Trinity College, Dublin

13:00 - 14:15

Lunch Break



Programme

Saturday 21st October 2006 (Afternoon)

Session 4

Case Histories

Chairperson: Professor Philip Mayne, Children's University Hospital, Temple St., Dublin

Panel: Dr. Sean Cunningham, St. Vincent's University Hospital, Dublin
Dr. Nuala Mc Carroll, St. James's Hospital, Dublin

14:15 - 14:45

EQAS for Interpretative Comments in Clinical Biochemistry
Dr. Gordon Challand, Royal Berkshire Hospital, Reading

14:45 - 15:15

Acute, Severe Refractory Hypoglycaemia
Ms. Ger Collier, Department of Biochemistry, St Vincent's University Hospital, Dublin

15:15 - 15:45

Case of Noninsulinoma Pancreatogenous Hypoglycaemia Syndrome (NIPHS)
Associated with Fasting Hypoglycaemia
Dr. Kheng Teong Lim, Department of Biochemistry, St James's Hospital, Dublin

15:45 - 16:15

Tea/Coffee Break

16:15 - 16:35

A Case of Hypophosphataemic Bone Disease due to Tumour Induced Osteomalacia
Dr. Jennifer Brady, Departments of Metabolism and Investigative Endocrinology, St Vincent's University Hospital, Dublin

16:35 - 16:55

TSH Secreting Pituitary Adenoma as a Cause of Abnormal TFTs.
Dr. Mohammed Adrees, Department of Biochemistry, St James's Hospital, Dublin

16:55 - 17:15

"Catch the Pigeon"
Dr. Alison Griffin and Ms. Paula O'Shea, Department of Chemical Pathology, Beaumont Hospital, Dublin

Saturday 21st October 2006 (Evening)

19:00 - 19:45

Pre Dinner Drinks Reception

20:00 - Late

Annual Dinner
Music by 'Deja Vu' Band



Speakers' Abstracts & Biography Session 1

'ETHICAL ISSUES'

Ethical Issues Concerning the Use of Human Biological Material

Dr Siobhan O Sullivan

ABSTRACT

Human Biological Material is a vital component of biomedical research. Ethical procurement and use of such material can promote scientific advances and contribute to the wellbeing of individuals and society as a whole. Central to the ethical conduct of research involving human subjects is informed consent. It encompasses a procedure that begins with the initial contact and carries through to the end of the involvement of subjects in research.

Concerns arise when obtaining human biological material for research from individuals in a clinical setting. The individuals' stress levels may be higher than normal in such circumstances and this may make it difficult for them to make complex decisions regarding issues not directly related to their clinical care. Since the basic premise for valid consent is the capacity of the patient to understand what is being proposed it is imperative that investigators distinguish clearly between medical treatment and medical research.

At the time of requesting consent, the investigators may not always know what, if any, future uses they would like to make of the material. The consent form should be layered so that prospective research participants could select from a graduated set of consent options so that, for example, in addition to the participant being asked to consent to participation in a specified research study, individuals would be offered options with respect to the use, storage and future use of their material. Use of archival biological material that can be traced back to an individual is controversial.

There is an onus on an investigator to seek consent from that individual (or next of kin) to use their biological material for a purpose other than that for which it was collected. In this way, the autonomy of and respect for persons is safeguarded.

Where it is not practicable to obtain consent from individuals for use of their archival material for research, research ethics committees may waive the requirement for consent.

Given the immense sensitivity of health-related information, it is imperative that those responsible for collecting and maintaining biological material (the custodian) should control access to this material for the duration of its use. The custodian should release material only to those who can provide evidence of ethical approval (a copy of which should be kept by the custodian) and who accept the same requirements for confidentiality. The custodian is responsible for making the material/data unidentifiable prior to release to a third party in the interests of protecting the individual from whom the material originated.

BIOGRAPHY

Dr. Siobhán O' Sullivan is the scientific director of the Irish Council for Bioethics (2002-present). She completed her PhD in Asthma and Allergy in Karolinska Institutet, Stockholm in 1998 and lectured in Immunology and Molecular Pathology in University College London (2000-2002), where she had a research group, looking at the inflammatory mechanisms in asthma. The Irish Council for Bioethics was established in 2002 as an independent, autonomous body to consider the ethical issues raised by developments in science and medicine.



Speakers' Abstracts & Biography

Consent and Confidentiality for Clinical Procedures, Legal Implications.

Dr. Asim A. Sheikh B.A., LL.M.,
Barrister-at-Law and Lecturer in Forensic and Legal Medicine,
UCD, Belfield.

ABSTRACT

This presentation discusses the doctrine of consent and confidentiality in clinical practice. It will discuss the legal theory and its practical applicability to clinical procedures. The presentation will look at case examples and problem areas in clinical practice and will suggest some practical solutions for clinicians.

BIOGRAPHY

Asim A. Sheikh is a practising Barrister specialising in healthcare law and clinical negligence. He graduated from the University of Limerick where he pursued a B.A. in European Studies with Law and Spanish followed an LL.M. (Masters in law) thesis by research, the topic of which was "Human Genetics: The Ramifications for Law & Ethics". He continued his education at the King's Inn, Dublin and was called to the Bar in 1998. He joined Forensic and Legal Medicine, University College Dublin in 1997 and is currently Lecturer in Legal Medicine.

He is Course Co-ordinator of and lectures on the postgraduate Higher Diploma in Healthcare (Risk Management). He is also Module Director of Legal & Ethical Aspects of Healthcare, which is taught on the MBA in Health Services Management, at the Royal College of Surgeons of Ireland, University College Dublin and the Michael Smurfit School of Business. He also lectures on the law module of the Diploma in Safety, Health and Welfare at Work at UCD, on the MSc in Healthcare Ethics and Law at the Royal College of Surgeons of Ireland and on the modules on Medical Law and Biotechnology Law on the Professional Course at the Law Society of Ireland. He also acts as external examiner in Medical Jurisprudence to the Department of Histopathology, Faculty of Medicine, TCD.

He is a member of the Irish Council for Bioethics and is currently a Rapporteur on the Council's working group on Advance Directives. He was Chair of the Council's Working Group on Human Biological Samples. He is a member of the Research Ethics Committee (REC) of the Health Research Board. He is a member of the World Association of Medical Law, the Irish Society of Human Genetics, and of the Irish Association of Law Teachers.



Speakers' Abstracts & Biography

Stem Cells: Biology and Ethics

Professor Frank Barry

Regenerative Medicine Institute, National University of Ireland, Galway

ABSTRACT

Stem cells have been isolated from a wide variety of tissues and, in general, their differentiation potential may reflect the local environment. They lack tissue-specific characteristics but under the influence of appropriate signals can differentiate into specialized cells with a phenotype distinct from that of the precursor. It may be that stem cells in adult tissues are reservoirs of reparative cells, ready to mobilize and differentiate in response to wound signals or disease conditions.

Mesenchymal stem cells (MSCs) have been isolated from periosteum, trabecular bone, adipose tissue, synovium, skeletal muscle and deciduous teeth. These cells have the capacity to differentiate into cells of connective tissue lineages, including bone, fat, cartilage and muscle. A great deal has been learned in recent years about the isolation and characterization of MSCs, and control of their differentiation. These cells have generated a great deal of interest because of their potential use in regenerative medicine and tissue engineering and there are some dramatic examples, derived from both pre-clinical and clinical studies that illustrate their therapeutic value.

This presentation will summarize recent findings regarding the potential clinical use of MSCs in cardiovascular, neural and orthopaedic applications. As new methods are developed, there are several aspects to the implanted cell-host interaction that need to be addressed before we can fully understand the underlying mechanisms. These include the host immune response to implanted cells, the homing mechanisms that guide delivered cells to a site of injury and the differentiation in vivo of implanted cells under the influence of local signals.

Human embryonic stem (ES) cells have been isolated in recent years and differ from adult stem cells in their differentiation potential and the range of cells types that arise. There are significant ethical obstacles surrounding the procurement and use of human ES cells. It is possible that human ES cells may have broader therapeutic potential compared to adult stem cells. However, the true therapeutic potential of ES cells is currently untested while the clinical utility of adult stem cell has been assessed in a number of early stage clinical studies. The potential benefits, obstacles and timelines of human stem cell therapy will be discussed.

BIOGRAPHY

Frank Barry is the Scientific Director of the Regenerative Medicine Institute (REMEDI), a Science Foundation Ireland-funded Centre for Science and Engineering Technology at the National University of Ireland, Galway. He is also Professor of Cellular Therapy at NUI Galway. He was born in Cobh, Co. Cork, studied science at University College Cork and received a Ph.D. in Biochemistry in 1984. He recently returned to Ireland after spending 14 years working in stem cell research at a number of institutions in the USA. He has held research and teaching positions at the Kennedy Institute for Rheumatology, London, University College Cork, Shriners Hospital for Children, Tampa, FL, the University of South Florida College of Medicine, Tampa, FL, Case Western Reserve University, Cleveland, OH and Osiris Therapeutics Inc., Baltimore, MD. His current research interests include the basic biology and therapeutic applications of stem cells in the areas of arthritic diseases and joint injury, tissue engineering applications in orthopaedic medicine and stem cell and gene therapy in cardiac repair. He has been a lecturer at the Kennedy School of Arts and Sciences graduate program in Biotechnology at Johns Hopkins University, Baltimore, is involved in several international and national research projects in cellular therapy and has served on the board of several international societies.

The research efforts underway at REMEDI centre on the use of adult stem cells for the treatment of human diseases. The current focus includes cardiovascular diseases, orthopaedics and neuronal repair. Scientist at REMEDI are developing methods for the isolation, expansion and characterization of these cells from human bone marrow, and are looking at stem cell delivery as a means of stimulating repair or regeneration of diseased tissues. In addition, the use stem cell-mediated delivery of therapeutic genes in selected disease targets is being assessed.



Speakers' Abstracts & Biography Session 2

'FROM MOLECULES TO MIGRATION'

Clinical Applications of Tandem Mass Spectrometry

Mr. Richard Walsh

Biochemistry Department, Children's University Hospital, Temple Street, Dublin 1

ABSTRACT

Mass spectrometry is one of the oldest techniques in analytical chemistry, dating back to 1898! Despite this, it has only come into use in clinical biochemistry during the last 20 years, with tandem mass spectrometry appearing in hospital laboratories over the past 10 years. There were two main reasons for this: (1) lack of expertise - most clinical biochemists are not trained in mass spectrometry, and (2) cost - mass spectrometers are expensive, putting them beyond the reach of most clinical laboratories.

All this is changing, however. The instrumentation, both hardware and software, is becoming much more user-friendly and prices are dropping; nevertheless, tandem systems still start at €300,000 and head for the stratosphere thereafter! Most importantly, a large number of applications have been published in recent years in mainstream journals (such as "Clinical Chemistry"), meaning that the clinical biochemist no longer has to work up a method from first principles.

The end result is that tandem mass spectrometry has now become the method of choice in a number of areas, for laboratories that can afford it. These include the investigation of inborn errors of metabolism, therapeutic drug monitoring and toxicology. There is much research ongoing at present, especially in the area of proteomics applied to diagnosis, and many analytes previously measured by techniques such as spectrophotometry or immunoassay are now amenable to mass spectrometric analysis.

To summarise, if the pure compound is available for use as a standard, then that compound can be quantified by tandem mass spectrometry.

BIOGRAPHY

Richard (Dick) Walsh was educated in clinical chemistry at CIT, DIT and TCD. He trained at Waterford Regional Hospital (then known as Ardkeen Hospital) a very long time ago! From here he moved to Our Lady of Lourdes Hospital, Drogheda, where he spent 14 years; the last 6 in charge of the biochemistry and endocrinology laboratories.

In 1990 he turned down the choice of a career change to cell biology in sunny San Diego and instead opted for the post of Principal Biochemist at The Children's Hospital (better known as Temple Street) in rainy Dublin, where he has remained ever since. Here he was instrumental in setting up Ireland's first clinical mass spectrometry laboratory, initially using gas chromatography - mass spectrometry (GC-MS) for urinary organic acid analysis, and more recently electrospray tandem mass spectrometry (ESI-MS-MS) for blood acylcarnitine profiling and phenylketonuria monitoring.

The Temple Street laboratories are now well-equipped with state-of-the-art mass spectrometers, having two GC-MS systems and two tandem mass spectrometers, one of which is dedicated to the National Newborn Screening Programme.

His main leisure interests are boating and hill-walking, strange hobbies for someone who can't swim and suffers from vertigo!



Speakers' Abstracts & Biography

Expanded Newborn Screening Programmes and Disease Definition

Professor Rodney Pollitt

Sheffield Children's (NHS) Foundation Trust

ABSTRACT

Since the introduction of universal newborn screening for phenylketonuria (PKU) in the USA and Europe in the late 1960's the growth in the number of conditions included remained relatively slow until the mid 1990's. In most countries this was typically around two/three by 1995 and included congenital hypothyroidism and a selection from cystic fibrosis, homocystinuria, tyrosinaemia type 1, galactosaemia and possibly Duchenne muscular dystrophy. Each of these were assayed using distinct and different methods and technological approaches.

The situation changed in the early 1990's initially with the advent of MS-MS analysis with fast atom bombardment and more latterly in 1995 with electrospray ionisation as means of sample introduction provided the potential not only to conveniently screen for PKU but up to thirty additional disorders simultaneously. In response there have been examples from around the world where countries have either proved overly cautious or in some cases overly eager to embrace the potential of this new application. In this presentation we will review the current situation in Europe and North America considering the criteria and processes, which may allow an appropriate population specific selection to be achieved. We will consider in detail the lessons that have been learned from the UK MCAD pilot scheme that may be applied in relation to other conditions and recommend candidate disorders for early inclusion in extended screening.

BIOGRAPHY

Rodney Pollitt trained as an organic chemist and was then employed by the UK Medical Research Council for 27 years, mainly in their Unit for Metabolic Studies in Psychiatry. Developed a particular interest in the diagnosis of inborn errors of metabolism and eventually moved to the National Health Service to work on this full-time. Has run the local newborn screening programme since 1969, becoming increasingly involved in screening issues in recent years and for a while serving as co-ordinator for the new UK-wide screening programme for cystic fibrosis.



Speakers' Abstracts & Biography

Genetics, Population History and Inherited Disorders in Ireland

Professor David T. Croke

Molecular & Cellular Therapeutics and RCSI Research Institute

Royal College of Surgeons in Ireland.

ABSTRACT

The Irish population exhibits the highest incidence in Europe of a number of common genetic disorders (some monogenic, some multifactorial), including cystic fibrosis, phenylketonuria, haemochromatosis and coeliac disease. It is apparent also that many of these disorders exhibit distinct allelic spectra (the number and frequency of causative gene variants) in Ireland when compared to mainland Europe. Genetic factors including founder effect, low effective population size and genetic drift, coupled with relative isolation, may account for the distribution of many mutations within the Irish population. Inherited metabolic disorders offer useful insights into the factors that have shaped this Irish 'disease burden', since disease-specific incidence values and mutation spectra are available across Europe as a result of newborn screening programmes. Phylogenetic and phylogeographic analyses of the R408W-1.8 mutation in Phenylketonuria and the Q188R galactosaemia mutation illustrate the roles played by founder effect and population expansion in determining the current incidence of these diseases in Ireland.

BIOGRAPHY

David Croke is a graduate of the University of Dublin (Trinity College) in Biochemistry and Genetics and is a Fellow of the Royal College of Pathologists. Following post-doctoral appointments as an EMBO Research Fellow at the Muséum National d'Histoire Naturelle (Paris) and as a consultant to the Biotechnology Division of the United Nations International Development Organisation (Vienna), he joined the staff of the Medical School of the Royal College of Surgeons in Ireland where he is Professor of Biochemistry. His research interests include inherited disorders of metabolism in Ireland and Europe and the genetics of the Irish Traveller population.



Speakers' Abstracts Session 3

'NEUROSCIENCE'

Neuroimaging as a Diagnostic Tool

Dr. Stephanie Ryan

Children's University Hospital, Temple St., Dublin

ABSTRACT

The brain may be imaged by ultrasound in infancy, and at any age by CT or MRI. This lecture will use the MR imaging evaluation of inherited metabolic disorders as an example of the use of neuroimaging as a diagnostic tool. Some conditions have characteristic imaging findings. In many conditions the MR imaging findings are less specific but narrow the differential diagnosis and guide biochemical and other testing towards the definitive diagnosis.

In addition to producing an image of the brain, MR can also be used to investigate the biochemistry of the brain. One can simply select an area of interest in the image of the brain and then by MR spectroscopy one can get information on the biochemistry within this part of the brain. MR spectroscopy can detect and measure the relative concentration of certain chemical compounds. The resultant MR spectroscopic findings may be diagnostic, such as in Canavan's disease. This is true for few conditions at present however. MRS may give less specific but nonetheless very useful diagnostic information in other conditions. The finding of lactate in the brain in an infant being investigated for severe developmental delay, for example, strongly points towards a mitochondrial disorder. The presence of lactate in the brain of a neonate with hypoxic ischaemic encephalopathy has very useful prognostic significance. MR spectroscopy may be used as a marker of activity of a disease such as adrenal leukodystrophy before the imaging part of the MR study is positive. This can help plan the timing of early bone marrow transplant in such a patient. Others have used MR spectroscopy to monitor this disease after bone marrow transplant.

The unique ability of MRI to image the brain and of MR spectroscopy to non-invasively measure a wide variety of metabolites in specified parts of the brain, when combined with serum and other biochemistry and the complete clinical picture, allows a greater understanding of disease and a greater degree of diagnostic accuracy than ever before possible.

References:

1. D D. M. Lin, T O. Crawford and P B. Barker: Proton MR Spectroscopy in the Diagnostic Evaluation of Suspected Mitochondrial Disease. *AJNR*. 2003 Jan;24(1):33-41
2. A.J. Barkovich^a, K Baranski, D Vigneron, J. C Partridge, D K. Hallam, B LHajnal and D M. Ferriero Proton MR Spectroscopy for the Evaluation of Brain Injury in Asphyxiated, Term Neonates *AJNR* 20:1399-1405 (9 1999)
3. Oz G, Tkac I, Charnas LR, Choi IY, Bjoraker KJ, Shapiro EG, Gruetter R Assessment of adrenoleukodystrophy lesions by high field MRS in non-sedated pediatric patients. *Neurology*. 2005 Feb 8;64(3):434-41.



Biography

BIOGRAPHY

Stephanie Ryan FRCSI, FFR RCSI, is a Consultant Paediatric Radiologist at the Children's University Hospital, Temple Street, Dublin and at the Neonatal Department of the Rotunda Hospital, Dublin 1. This position is wholly devoted to performance and interpretation of paediatric imaging. At least 40% of her work is with neonates and most of this is neuroimaging.

Dr. Ryan trained in General Surgery and Radiology in Ireland and did specialist training in Paediatric Radiology in Seattle, Washington, USA and further training in Angiography and Interventional Radiology in the Mayo Clinic, USA. During that time she was awarded top prize among her peers, Investigator of the Year, by the North American Society for Paediatric Radiology. She was a consultant Paediatric Radiologist in the USA for several years before taking up her present position.

In addition to obtaining Fellowship of the Royal College of Surgeons and of the Faculty of Radiologists of that College, Dr. Ryan is Board Certified by the American College of Radiology and has been awarded Certificate of Added Qualification in Paediatric Radiology by that College.

Dr. Ryan has written several papers on paediatric imaging, written chapters in a textbook on neonatal imaging and has written a textbook on anatomy in diagnostic imaging, the second edition of which was published in 2004. She has presented papers and been an invited speaker at several international meetings on Paediatric Radiology.



Speakers' Abstracts & Biography

Investigation of Developmental Delay

Dr. Mary King

Children's University Hospital, Temple St., Dublin

ABSTRACT

Developmental delay occurs in 5-10% of children under 5 years. Global developmental delay is defined as a significant (performance of 2 or more standard deviations below the mean delay), in 2 or more developmental domains: motor, speech and language, cognition, emotional and social behaviour or activities of daily living. Isolated speech and language or motor delay or autism are not included in this definition. The yield from investigations is, not surprisingly, highest in children with severe global developmental delay but causes with genetic or therapeutic implications may be found in all degrees of delay. There are few evidence based guidelines for investigation of developmental delay in the literature and most units use a protocol based on consensus of expert opinion. This paper will review recent publications and our own experience in the investigation of developmental delay.

In the absence of positive family history, consanguinity, dysmorphism or coarsening of features, motor signs (hypotonia, "cerebral palsy", abnormal movements), abnormal head growth, epilepsy, stasis or regression of development, - the yield from investigations is low. Homocystinuria, mitochondrial disorders and Duchenne Muscular Dystrophy may have few clinical clues early on and are common in our population. In our experience Biotinidase deficiency and Fragile X Syndrome are extremely rare while Karyotype and subtelomeric studies in severe non specific delay have a high yield.

A guideline for investigations of global developmental delay in pre-school children will be proposed.

BIOGRAPHY

Dr. Mary King, Consultant in Paediatric Neurology at the Children's University Hospital, Temple St., Dublin. She previously worked in Yorkhill Hospital, Glasgow, Scotland before returning to Dublin. In the early 1980s she set up the department of neurology at the Children's Hospital. She also is a consultant neurologist to the Rotunda Hospital and Beaumont Hospital in Dublin



Speakers' Abstracts & Biography

Disorders of Dopamine and Serotonin Metabolism

Simon Heales

Neurometabolic Unit, National Hospital, Queen Square, London

ABSTRACT

A number of inborn errors of dopamine and serotonin metabolism are documented. To date, disruption of dopamine and serotonin metabolism is known to arise as a consequence of disrupted tetrahydrobiopterin (BH4) metabolism, aromatic amino acid decarboxylase deficiency and disorders of pyridoxal phosphate metabolism. Isolated deficiencies of dopamine metabolism arise from tyrosine hydroxylase deficiency and a specific impairment of serotonin metabolism would be predicted to occur as a result of tryptophan hydroxylase deficiency.

Many of these disorders can be identified by cerebrospinal fluid (CSF) analysis, i.e. the above disorders give a diagnostic "signature" of metabolites. Furthermore, CSF analysis allows for monitoring the efficacy of treatment regimes targeted at enhancing central monoamine metabolism. Correct sample collection, storage and transport procedures must be adhered to when investigating patients for this group of disorders. In addition, clinical and drug treatment details should accompany the samples.

A central deficiency of folate is also known to occur with a clinical presentation that can overlap with that of the disorders of dopamine/serotonin metabolism. Consequently, analysis of CSF 5-methyltetrahydrofolate is often requested, i.e. in addition to dopamine, serotonin and tetrahydrobiopterin metabolites.

BIOGRAPHY

1987 PhD Biochemistry (Aston University, Birmingham). Currently Consultant Clinical Scientist and Deputy Director of the Neurometabolic Unit, National Hospital (University College London Hospitals Foundation Trust), Queen Square, London. Specialist interests; (a) Inborn errors of dopamine, serotonin and tetrahydrobiopterin metabolism. (b) Inherited and acquired disorders of mitochondrial function. Diagnostic activities, for this group of disorders, are enhanced by external grant funded research that is evaluating novel treatment regimes for tetrahydrobiopterin deficiency and evaluating the effects of oxidative/nitrosative upon mitochondrial function. Part of this research is performed at the Institute of Neurology (University College London) where I hold an Honorary Readership. Most importantly, I have three lively daughters (Aged 14,12 & 9) that keep me on my toes !



Speakers' Abstracts & Biography

Targeting Alzheimer's disease -
amyloid β -protein disruption of synaptic plasticity

Professor Michael Rowan

Dept. Pharmacology & Therapeutics, Trinity College, Dublin

ABSTRACT

Alzheimer's disease can be viewed as a protein misfolding disease. Inappropriate processing of the proteolytic fragment of amyloid precursor protein, amyloid β -protein ($A\beta$), in early stages of the disease may lead to the release of stable small oligomers that are highly mobile with the potential to be more toxic than larger fibrillar assemblies.

Recently, the importance of such soluble species of $A\beta$ in triggering synaptic dysfunction, long before neuronal loss occurs, has become apparent. Animal models have revealed that plasticity of hippocampal excitatory synaptic transmission is relatively selectively vulnerable to $A\beta$ both in vitro and in vivo. This presentation focuses on the mechanisms of $A\beta$ inhibition of long-term potentiation (LTP) at synapses in the rodent hippocampus from two complimentary perspectives.

First, we will examine evidence that the synaptic plasticity disrupting effect of this peptide resides primarily in oligomeric rather than monomeric or fibrillar $A\beta$ species. Cell-derived $A\beta$ oligomers can be purified with size-exclusion chromatography and shown to inhibit LTP at subnanomolar concentrations. Exogenously applied and endogenously generated antibodies that can avidly bind $A\beta$ oligomers can protect against the inhibition of LTP by directly neutralizing them in the brain.

Second, the importance of different oxidative/nitrosative stress-linked cascades including JNK, p38 MAPK and NADPH oxidase/iNOS-generated reactive oxygen/nitrogen free radicals in mediating the inhibition of LTP by $A\beta$ will be evaluated. Selective inhibitors of these cascades can abrogate the inhibition of LTP by $A\beta$. Remarkably, agents that reduce the levels of the cytokine Tumor Necrosis Factor (TNF) are also protective and mice deficient in type 1 TNF receptors are resistant to the inhibition of LTP by $A\beta$.

Such mechanistic studies provide a plausible explanation for the sensitivity of hippocampus-dependent memory to impairment in early Alzheimer's disease patients. Mechanism-based therapeutic strategies targeting $A\beta$ oligomers and pro-inflammatory synaptic stress provide an attractive strategy in the control of early Alzheimer's disease.

BIOGRAPHY

Prof Michael Rowan has been a lecturer in Pharmacology since 1979 at Trinity College Dublin. He graduated from UCD in 1976 with a BSc and from TCD in 1981 with a PhD. He has over 100 original Neuroscience publications in international journals.



Speakers' Abstracts & Biography Session 4

'CASE HISTORIES'

EQAS For Interpretative Comments in Clinical Biochemistry

Dr. Gordon Challand

Royal Berkshire Hospital, Reading

ABSTRACT

'Cases for Comment', an interpretative exercise in Clinical Biochemistry, began distribution through the general mail base of the Association for Clinical Biochemistry in 1997. Comments made by participants were broken down into components which were scored by peer review. After 100 cases, this was developed into a formal EQAS which started distribution in 2001.

The EQAS is available through a web site accessible through the home page of UKNEQAS ([HYPERLINK "http://www.ukneqas.org.uk"](http://www.ukneqas.org.uk) www.ukneqas.org.uk); around 23 cases are distributed annually. Participants have two weeks to make a short interpretative comment on each Case. Whole anonymised comments are then scored on a scale from -1 to +3 by assessors working independently; the mean score then enables all comments to be ranked. A summary of each case including background, outcome where known, and examples of low, median and high scoring comments is made available to participants through the web site. Participants are given the score for their own comment and their running score over previous comments compared with all participants.

The scheme has proved popular and there are currently more than 300 individual and group participants. Initially there was some opposition to comment scoring, but this is now quite well accepted. With time, the proportion of comments receiving zero or negative scores has markedly reduced. Several of the cases have led to further internet discussion. The Cases are widely used as an educational resource.

Scoring whole comments is undoubtedly more controversial than scoring components, but avoids the subjective element inherent in component selection and tests communicative as well as interpretative skills. There has been an overall improvement in the standard of comments, and several difficult areas of interpretation, of definition and of ethics have been clarified. I believe that such schemes are as vital to improvements in laboratory performance as conventional analytical EQA.

BIOGRAPHY

Gordon Challand started his career in Clinical Biochemistry at St. Bartholomew's Hospital, London in 1971, and after working at the Glasgow Royal Infirmary, Addenbrooke's and the Charing Cross Hospitals, moved to the post of Consultant Biochemist at the Royal Berkshire Hospital in 1985. He has twice before been asked to give talks at ACBI meetings. Author of more than 100 publications, he was awarded the President's Shield of the Association for Clinical Biochemistry in 1999 for outstanding achievements in education, and in 2005 was elected Emeritus Member. He is also Honorary Professor of Laboratory Medicine in the University of West China.



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O'Shea E¹, Awadalla A², Macken S², Gormally S³, Monavari A², Mayne P¹.
¹Biochemistry Department, ²National Centre for Inherited Metabolic Disorders, Children's University Hospital, Temple Street, Dublin 1 and ³Our Lady of Lourdes Hospital, Drogheda.

Title: Plasma BNP and NT-proBNP levels in 'normal' premature infants

Authors: Farombi-Oghuvbu I¹, Guerin H², Mayne PD², Corcoran D¹, Matthews T¹.

Address: ¹Departments of Neonatology and ²Clinical Biochemistry, Rotunda Hospital, Dublin 1

INTRODUCTION

B-type natriuretic peptide (BNP) is released from the heart in response to blood volume overload or ventricular dilatation. It is synthesized as a prohormone (134 amino acids) and cleaved initially to proBNP (108 aa) and then to biologically active BNP (32 aa) and a degraded fragment NT-proBNP (76 aa). A pilot study was undertaken to compare BNP and NT-proBNP levels in premature infants as a preliminary study to a larger one to determine their usefulness as markers of cardiac function in preterm infants.

METHODS

Informed consent was obtained from parents of 10 preterm infants, born <34 weeks gestation and weighing <2kgs. Blood samples were collected on Days 1, 3 and 5 of life for BNP (Abbott Axsym®) and NT-proBNP (Roche Elecsys®) measurement. Simultaneous echocardiography, blood pressure and core and peripheral temperatures were recorded as markers of cardiac function.

RESULTS

Seven of the 10 infants had clinically 'normal' cardiac function for age. Serum BNP and NT-proBNP levels fell over the first five days of life ($p < 0.001$). Pearson correlation between BNP and NT-proBNP for all infants ($n=10$) over the first five days of life (total analyses=28) was 0.96 ($p < 0.001$). Inter-assay CV for BNP ($N=8$) was 4.4% at 118 pg/mL and for NT-proBNP ($N=14$) 0.81% at 2120 pg/mL.

CONCLUSION

BNP and NT-proBNP are high at birth and fall significantly over the first 5 days of life in the premature infants with clinically 'normal' cardiac function.

Title: Comparison of eGFR calculated by 3 Variations of the 4-variable MDRD formula

Authors: Stapleton MT, McCarthy K, Boland L and O Mullane J.

Address: Biochemistry Department, Cork University Hospital

AIM

The aim of this study is to compare eGFR values calculated by (1) the original 4-variable formula, (2) NEQAS, (3) WEQAS variations of this.

METHODS

120 creatinine results selected from daily GP requests (36 females, 84males). Creatinine was measured on the Olympus 5400 analyser using the kinetic Jaffe reaction.

GFR was estimated by the following formulae

1. $186 \times (\text{Creatinine} \times 0.011312) - 1.154 \times \text{age} - 0.203 \times 0.742$ (if female)
2. $175 \times [((\text{Creatinine} - 16.14)/0.955) \times 0.011312] - 1.154 \times \text{age} - 0.203 \times 0.742$ (if female)
3. $175 \times [((\text{Creatinine} - 11) \times 1.04) \times 0.011312] - 1.154 \times \text{age} - 0.203 \times 0.742$ (if female)

Passing-Bablok regression analysis was calculated and Altman-Bland bias plots were generated using Analyse-It software.

RESULTS

Median and range Creatinine concentration was 97 (61 -189) $\mu\text{mol/L}$. Regression equations were as follows:

Formula 1 v Formula 2: $y = 1.283x - 12.81$

Formula 1 v Formula 3: $y = 1.133 - 6.93$

Formula 2 v Formula 3: $y = 0.892 + 3.45$

CONCLUSIONS

Estimated GFR varies depending on the formula used to calculate it. Prior to laboratories providing GFR estimates, there should be consensus on which formula is used.

Title: An Audit of Hyperhomocysteinaemia in Women who have Suffered Adverse Pregnancy Outcomes

Authors: Collier G, Healy L, Fleming CA, Murphy K and Cunningham SK.

Address: Department of Biochemistry and Haematology, St. Vincent's University Hospital, Dublin

INTRODUCTION

Venous Thrombophilic disease is a major contributor to pregnancy morbidity with potentially serious adverse effects for mother and foetus. Maternal thrombophilias increases the risk of an adverse pregnancy outcome. Women with a raised total Homocysteine level have a heightened risk of venous thromboembolism (VTE) and poor pregnancy outcomes.

AIM OF THE STUDY

Our objective was to audit the frequency of hyperhomocysteinaemia in women who have suffered recurrent pregnancy loss.

METHODS

Current guidelines recommend thrombophilia screening including homocysteine levels in women with previous V.T.E , recurrent miscarriages and unexplained poor pregnancy outcomes. Homocysteine was measured by FPIA on the Abbott IMx in Biochemistry Department. The other markers were measured in the Haematology Department.

RESULTS

Screening was carried out on 129 women who had suffered adverse pregnancy outcomes. The majority of these women (54%) having had recurrent miscarriages. 26 % of patients screened had one or more abnormal markers for thrombophilia. 3.8% of these had a homocysteine > 15umol/l, (reference range 5-15 umol/l). The elevated homocysteine levels ranged from 16.2-64.2 umol/l. One patient was homozygous for MTHFR mutation. The literature states that a combination of a high homocysteine and FV Leiden mutation increases the risk of thromboembolism. None of the patients studied had such a combination.

DISCUSSION

In our study one patient who had three miscarriages had a successful pregnancy following the reduction in her homocysteine level from 64.2 umol/l to 13.9 umol/l. Despite the low incidence of hyperhomocysteinaemia in this patient cohort screening for hyperhomocysteinaemia may be justified because of the potential benefit of treatment.

Title: A Multifactorial Case of Hepatitis in Infancy

Authors: Fitzsimons PE¹, Cotter M¹, Rizvi S² and Mayne PD¹.

Address: Departments of ¹Pathology, and ²Paediatrics, Children's University Hospital, Temple Street, Dublin 1

INTRODUCTION

An 8 month old boy presented with a 3 day history of upper abdominal pain, diarrhoea, lethargy, pallor, pyrexia and poor feeding. On examination, he had hepatosplenomegaly and generalised lymphadenopathy. Initial differential diagnosis included viral hepatitis and ALL.

LABORATORY INVESTIGATIONS

Renal function normal; TP 60 g/L (60-80); Alb 33 g/L (36-55); ALP 476 U/L (60-580); ALT 121 U/L (0-67); AST 120 U/L (0-54); BILIT 23 $\mu\text{mol/L}$ (0-17); BILIC 12 $\mu\text{mol/L}$ (0-5); CRP 36 mg/L (0-10). Blood film showed anemia, lymphocytosis, neutropaenia, and atypical lymphocytes. There was persistent elevation of plasma transaminases, LDH, triglycerides (3.4 mmol/L) and ferritin (415 $\mu\text{g/L}$), with progressive cholestasis. The child became progressively anaemic and leucopenic. Bone marrow aspirate revealed prominent lymphocytosis, histiocytes and occasional haemo-phagocytic forms. Serology and PCR was positive for EBV.

DIAGNOSIS

X-linked Lymphoproliferative Syndrome (XLP) with haemophagocytic syndrome (HLH) precipitated by EBV.

Acquired and familial HLH causes a highly stimulated but ineffective immune response to viral infection. Familial HLH is characterized by high levels of soluble IL-2 receptor α chain, impaired NK cell and cytotoxic T-cell function; XLP is characterised by a predisposition for EBV associated HLH leading to uncontrolled lymphoproliferation of T cells and macrophages.

The child is responding to immunosuppressive /cytotoxic drugs and is awaiting BMT. This case highlights the importance of the awareness of the clinical symptoms and diagnostic criteria for HLH/XLP to enable prompt life-saving treatment.

Title: Use of biochip array technology for neurological research applications

Authors: Rodríguez M L, Brennan L, FitzGerald SP, and McConnell RI.

Address: Randox Laboratories Ltd. 55, Diamond Road, Crumlin, Co Antrim, BT29 4QY, Northern Ireland

AIM

The aim of this study is to demonstrate the applicability of biochip array technology to the simultaneous measurement of analytes associated with nervous system dysfunction and found in body fluids.

METHOD

The methodology is based on immunoassays, the capture biomolecules are immobilised and stabilised on the biochip surface (9 mm²) forming defined microarrays of discrete test regions (DTRs). The biochip is also the reaction platform where the immunoreactions take place. After addition of sample and detection of the analyte with a chemiluminescent detector, a cooled charged couple device (CCD) camera simultaneously detects the signals produced in the different DTRs of the biochip. The application to the Evidence Investigator™ analyser, leads to automatic imaging and data processing by the system software.

RESULTS

Twelve cytokines were simultaneously measured with the cytokine array, with analytical sensitivity ranging from 0.8 pg/ml (IL-1 alpha) to 14.6 pg/ml (VEGF). The adhesion molecules array measured in real time, five soluble adhesion molecules at levels lower than the minimum value for the reference range. Six analytes were simultaneously detected with the cerebral array I with measuring ranges from 0-500 pg/ml (IL-6) to 0-15 µg/ml (CRP). Eight other analytes were detected at the same time with the cerebral array II. All the assays in the biochip arrays showed good intra-assay and inter-assay precision typically CV≤10% and recovery between 70-120%.

CONCLUSION

This technology is a valuable tool for the detection of multiple analytes in real time with a single sample. The miniaturization of assay procedures reduces consumption of sample and reagent volume, which is of interest in research applications.

Title: Tyrosinaemia Type 1: The first Irish case

Authors: Charleton N¹, Manning R², Deverell D¹, Walsh R¹, Mayne P.D¹.

Address: ¹Biochemistry Department and ²National Centre for Inherited Metabolic Disorders, Children's University Hospital, Temple Street, Dublin

INTRODUCTION

The hereditary tyrosinaemias are a group of inherited disorders of tyrosine catabolism. The most clinically severe of these is type 1 (OMIM 276700), which has an estimated worldwide incidence of 1:100,000; in spite of these factors no case had been recorded in Ireland until February 2006. Type 1 is caused by a deficiency of the enzyme fumarylacetoacetate hydrolase (FAH), which catalyses the final step in the degradation of tyrosine.

CLINICAL PRESENTATION

The patient presented at 2 weeks of age to another hospital with E coli sepsis secondary to a UTI, with associated hypoglycaemia. A hypoglycaemia work-up was carried out, which included urinary organic acid analysis.

LABORATORY FINDINGS

Urinary organic acid analysis showed markedly increased excretion of succinylacetone and succinylacetoacetic acid; these metabolites are pathognomic for tyrosinaemia type 1. This sample had a tyrosine concentration of 169 $\mu\text{mol}/\text{mmol}$ creatinine (reference range 0 - 31). A follow-up plasma tyrosine was 495 $\mu\text{mol}/\text{L}$ (reference range 0 - 196).

OUTCOME

Tyrosinaemia type 1 is treated with nitisinone, a specific pharmacotherapy. At the most recent clinical review, some 7 months after diagnosis, the patient was found to be thriving and developing normally.

Title: Study of the Occurrence of Buprenorphine Use in a Cohort of Patients Attending Drug Treatment Centres using Enzyme Immunoassay

Authors: Maguire R, Lawlor L.

Address: Drug Treatment Centre Board, Pearse St., Dublin 2

INTRODUCTION

Buprenorphine (Subutex®, Bu Trans®, Transtec®) is a semi-synthetic analgesic derived from thebaine. It was first marketed as an analgesic in the early '80's. It is now also used as a popular substitution treatment for opioid addiction throughout Europe. Buprenorphine acts as a partial agonist binding at the μ -opioid receptor. Stimulating these receptors mimics morphine-like effects, such as analgesia and euphoria. As a result buprenorphine can be subject to abuse. ¹

In 1992/93 a survey of South Western France community pharmacists was carried out. It listed buprenorphine as the third highest addiction potential of prescription medicines. The abuse potential of buprenorphine has been estimated in France as high as 20-30% in substitution treatment subjects. ²

In Ireland buprenorphine can be prescribed as an analgesic in the form of transdermal patches or more recently as a substitution treatment (sublingual tablets) for opioid addiction.

METHOD

Buprenorphine use may be detected in urine using the CEDIA® Buprenorphine Assay, a homogenous enzyme immunoassay system. The technology genetically engineers bacterial enzyme β -galactosidase into 2 fragments. These fragments only become active upon reassembly, cleaving a substrate, which causes a colour change that can be measured (absorbance). The absorbance observed is proportional to the quantity of buprenorphine present in a sample.

100 urine samples from patients in the Drug Treatment Centre, Pearse St, were selected and analysed for buprenorphine. A buprenorphine cut-off calibrator containing 5ng/ml buprenorphine was used.

RESULTS

8 of the urine samples analysed were positive using the CEDIA® Buprenorphine Assay.

4 of the positive urine samples were sent for GC/MS confirmation to COZART, Oxfordshire, UK. The remaining four samples had insufficient volumes to be confirmed.

Three of the four urine samples analysed by GC/MS were confirmed positive for buprenorphine.

None of the patients were prescribed buprenorphine as an opioid substitute at time of analysis.

REFERENCES

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2. Report to the NACD on "Use of Buprenorphine as an intervention in treatment of Opiate Dependence Syndrome", 2002



Title: Expanded Newborn Screening for Inherited Metabolic Disorders in Ireland - assessment of criteria

Authors: Mayne PD¹, Walsh R¹, Roche G¹, Treacy E².

Address: ¹National Newborn Screening Laboratory and ²National Centre for Inherited Metabolic Disorders, Children's University Hospital, Temple Street, Dublin 1

INTRODUCTION

The Wilson and Jungner criteria for screening, published in 1966, included among 10 criteria the incidence of the disorder and known natural history; the National Screening Committee (UK) and others have included an evidence based approach. The Irish Newborn Screening Programme included PKU, galactosaemia, homocystinuria, MSUD and tyrosinaemia (which was subsequently discontinued) based on the bacterial inhibition assay (BIA) and congenital hypothyroidism and congenital toxoplasmosis both immunoassays. Tandem mass spectrometry (TMS) was implemented in Ireland in 2005 to replace the BIA for the aminoacidopathies. TMS enables multiple disorders to be diagnosed with a single test; it has been introduced by a number of programmes worldwide in order to expand the repertoire of disorders, based on recommendations from such organisations as the Maternal and Child Health Bureau (USA).

Of the 24 disorders recommended, 717 individuals with 19 of these disorders currently attend the National Centre for Inherited Metabolic Diseases, Temple Street; 90% of these were diagnosed by the current programme. Expanded screening would have resulted in 72 additional cases being diagnosed in the presymptomatic phase with obvious benefits for some in clinical outcome.

The implementation of expanded newborn screening is feasible based on the current programme and would require no change to the pre-analytical phase. However, additional scientific and clinical staff would be required to cope with the extra analytical workload and the counselling of parents of false positive cases.

Title: Albumin Targets in End Stage Renal Disease (ESRD): Effect of Variation in Assay Methods

Authors: McGing P¹, Gillman B², Halton K¹, Moran AM³, Lineen J³, Mullins^{1,4}, O'Meara YM³, Maguire S¹, Kyne F¹.

Address: ¹Depts of Biochemistry, ²Nutrition & Dietetics, and ³Nephrology, Mater Misericordiae University Hospital, Dublin 7, and ⁴Cappagh Orthopaedic Hospital

INTRODUCTION

Serum albumin is an important predictor of morbidity and mortality in patients with ESRD. However, reported albumin values may vary with the analytical method used. Albumin is predominantly measured by an automated technique using one of two dye binding assays, BCP or BCG. The BCG method is used by the majority of renal units in the UK (75%) and in the Republic of Ireland (66%). In the Mater, albumin assays are performed using the BCP method. It was evident from audit data that a substantial proportion of our patients were not achieving the albumin target ($\geq 35\text{g/L}$), a measure of clinical efficacy. The current study was undertaken to see if this could be explained by the assay method employed.

MATERIALS AND METHODS

Serum albumin was measured by BCP and BCG in 37 samples from 28 haemodialysis patient, 5 samples from peritoneal dialysis patients, and in 17 control samples (OPD/GP 10, Acutely unwell inpatients 7).

RESULTS

Mean difference for all samples (BCG - BCP) was 4.8 g/L ($SD=1.9$). The magnitude of the mean difference was significantly greater in samples with an albumin level $< 30\text{g/L}$, versus albumin $> 34\text{g/L}$, (6.42 ± 1.98 v. 3.89 ± 1.36 $\{P<0.001\}$). Only 43% of haemodialysis samples had an albumin level within normal range using the BCP assay compared to 92% with the BCG assay.

DISCUSSION

Variations in albumin measurements may affect assessment of nutritional status, lead to inaccurate calcium measurements, and may interfere with its utility as an outcome predictor. Differences in assay methods and reference ranges must be taken into account when performing comparative audit, and in the interpretation and implementation of clinical practice guidelines.

Title: Evaluation of Total and Free Thyroxine Assays on the DPC Immulite 2000 immunoassay analyser

Authors: O’Kelly R, Barry S, O’Donnell A, Phelan M, O’Leary JJ.

Address: Biochemistry Dept., Coombe Women’s Hospital, Dublin 8

AIM

Total T4 (TT4) and Free T4 (FT4) assays were evaluated on the Immulite 2000 and compared to the Tosoh method (our referral method). TT4 and FT4 were assayed in maternity patients at different stages of pregnancy to see if a fall in Free T4 levels occurs in the third trimester as reported in the literature.

METHODS

TT4 and FT4 assays on Immulite 2000 were evaluated for precision and bias. Patient results from our method (chemiluminescence) and the referral method (fluorescent enzyme immunoassay) were compared. 189 consecutive maternity patients of known gestation (n = 61, 79 and 49 from 1st, 2nd and 3rd trimesters respectively) were tested for TT4 and FT4 on the Immulite 2000. Results were analysed using Analyse-It software (Passing-Bablok regression and independent samples t-test).

RESULTS

Within-batch CVs for 3rd trimester serum (n=10) were 4.4% for TT4 at 142nmol/L and 5.5% for FT4 at 15.3pmol/L. Between-batch for control material (n=30) CVs for TT4 were 9.0% at 32.5 nmol/L, 5.3% at 105 nmol/L and 6.2% at 164 nmol/L and for FT4 were 6.8% at 9.2 pmol/L, 3.7% at 15.9 pmol/L and 3.3% at 27.2 pmol/L. A comparison of Tosoh and Immulite results showed better correlation for TT4. TT4: y (Immulite) = $0.97(\text{Tosoh}) + 6.8$; FT4: y (Immulite) = $0.61(\text{Tosoh}) + 7.6$. No significant difference was seen for TT4 between trimesters, however a significant difference in FT4 was seen between 1st and 2nd (p= 0.0019) and 2nd and 3rd (p=0.0001).

CONCLUSION

TT4 and FT4 assays performed within specifications. FT4 correlated poorly with our referral method. Our limited study concurs with the literature finding that FT4 levels fall during pregnancy and thus trimester-specific reference intervals may be appropriate.

Title: An Audit on the use of CA15-3 in Breast Cancer

Authors: Mc Ging P¹, Sheikh R², Taqi A², McCaffrey j².

Address: Departments of ¹Biochemistry and ²Oncology, MMUH, Dublin 7

INTRODUCTION

The objective of this study was to establish whether measurement of CA15-3 contributed to improved patient care in our hospital.

METHODS

We reviewed clinical information from the charts of 176 patients attending the medical oncology unit in the Mater Misericordiae University Hospital between 1999 and 2005 for follow-up treatment of breast cancer.

CA15-3 was kindly assayed by Nuclear Medicine Laboratory, SVUH, Dublin (director Prof MJ Duffy). Cut off value for CA15-3 was 40kU/L.

RESULTS

A total of 100 patients remained disease free at follow-up (58%). Only 5 patients had CA15-3 values above 40 kU/L during follow-up (all <50kU/L). 95 patients had their CA15-3 values within normal range, a diagnostic specificity of 95%. Of the remaining 76 patients, 15 had metastatic disease at diagnosis while 61 developed metastases later. Of the 61 patients in whom metastases developed during subsequent (post-op) follow-up, CA15-3 was elevated in 39 patients (64%). Two patients with rising CA15-3 over a one-year period, but with negative radiology (CT and PET scan, mammogram, physical examination), eventually developed detectable metastases.

DISCUSSION

We found in this audit that CA-15-3 has a sensitivity value of around 64% and specificity of around 95% in breast cancer follow up. This agrees very well with the ASCO (American Society of Clinical Oncology) review, which reported 67% and 92% respectively. In patients without detectable metastases at diagnosis, the Positive Predictive Value for subsequent metastases was 89%; the Predictive Value of a negative CA-15-3 for continuing remission was 81%. Our conclusion is that CA-153 is a reliable marker in assessing the response to therapy. Further study is being undertaken to formulate a new protocol for use of CA-153 in our unit, with particular reference to its use alongside and / or in place of some radiological investigations.

REFERENCE

see Minireview by Prof MJ Duffy, in Clinical Chemistry, March 2006, pp345-51.

Title: Determination of Phenylalanine and Tyrosine in Dried Blood Spots by Tandem Mass Spectrometry.

Authors: O'Shea A, Walsh R, Keegan B, Conway H, Mayne PD.

Address: Biochemistry Department, Children's University Hospital, Temple Street, Dublin 1

INTRODUCTION

Phenylketonuria (PKU) due to the deficiency of the enzyme phenylalanine hydroxylase (PAH) and hyperphenylalaninemia due either to decreased PAH activity or deficiency of the cofactor tetrahydrobiopterin (BH4) leads to the accumulation of phenylalanine and depletion of tyrosine in blood. Untreated classical PKU results in severe brain damage with mental retardation, seizures, and spasticity. Newborn screening for PKU and hyperphenylalaninemia has been in operation in the Irish Republic since 1966.

AIM OF THE STUDY

The aim of the study was to set up a method to measure phenylalanine and tyrosine on dried blood spots (DBS) by tandem mass spectrometry and compare with our current serum method used to monitor already diagnosed patients.

METHOD

The method used was that of Turner et al. using underivatised samples. Blood spots were punched into microtitre plates and 150µl of methanol/water (83:17) containing deuterated internal standards was added. The mobile phase was acetonitrile/water (1:1) with formic acid (0.025%). Phenylalanine and tyrosine were measured on a Waters Quattro Premier tandem mass spectrometer. MRM for phenylalanine was 166/120 and deuterated phenylalanine 171/125. MRM for tyrosine was 182/136 and deuterated tyrosine 186/140

RESULTS

Within batch CV for both phenylalanine and tyrosine was 2.6 % (n=19).

Between batch CV for phenylalanine was 6.9 % and tyrosine 9.3 % (n=50), and the method was linear up to 1200 µmol/L. A comparison of DBS with serum showed a good correlation with $r^2=0.95$.

CONCLUSION

Measurement of phenylalanine and tyrosine in DBS samples is acceptable for monitoring patients. It has two advantages, one being easier collection of samples by patients and the other a large reduction in manual sample preparation in the laboratory.



Title: Uridine monophosphate synthase deficiency, type 2

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INTRODUCTION

Hereditary orotic aciduria (OMIM 25890, 25892) is a rare inherited disorder caused by deficiency of the bifunctional protein uridine monophosphate synthase (UMPS), an enzyme of the de novo pyrimidine biosynthetic pathway. The first function of the enzyme is an orotate phosphoribosyltransferase (OPRT) activity; a defect here causes UMPS deficiency, type 1. The second function of the protein is an orotidine-5'-monophosphate decarboxylase (ODC) activity; a defect here causes UMPS deficiency, type 2. This patient is only the fifth known case of type 2 UMPS deficiency.

CLINICAL PRESENTATION

The patient was referred for investigation of global developmental delay, hypoactivity and microcephaly.

LABORATORY FINDINGS

Urinary organic acid analysis showed a moderately increased excretion of orotic acid with a lesser excretion of uracil. Subsequent quantitative pyrimidine analysis showed markedly increased excretion of both orotic acid and orotidine. Analysis of the UMPS complex showed normal OPRT activity, but no ODC activity, confirming the diagnosis of UMPS deficiency, type 2.

OUTCOME

Uridine is the recommended treatment for UMPS deficiency. On this, the patient has shown improvements in activity, understanding and development.

Title: Associations between N-acetyltransferases genetic polymorphisms, meat consumption, smoking and colorectal cancer

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INTRODUCTION

N-acetyltransferase 2 (NAT2) is an enzyme involved in the metabolism of carcinogens and other mutagens such as the aromatic and heterocyclic amines present in cigarette smoke and red meat cooked by high-temperature. This enzyme is polymorphic, and the fast acetylator phenotype is thought to be a risk factor for some cancers.

AIM

The authors investigated the effect of differences in acetylation capacity, determined by NAT2 genotypes, on colorectal cancer risk associated with exposure to tobacco smoke or red meat consumption, known risk factors for colorectal carcinomas.

PATIENTS AND METHODS

This study, in Egypt, involved colorectal cancer patients (n=35), first degree family relatives (n=15) and controls (n=10). Interviews regarding lifestyle, medical history, and diet were conducted. DNA was extracted from peripheral lymphocytes obtained from whole-blood samples, and genotyping of NAT2 genetic polymorphisms was done using a fluorescence-based melting curve analysis method by real-time polymerase chain reaction (PCR). Fast, intermediate, or slow phenotypes were detected from the genotype.

RESULTS

Although there was no significant difference regarding the NAT2 genotypes distribution, there was a statistically significant difference in percent distribution of the NAT2*4 allele. The difference between patients and relatives was non-significant; while that between patients and controls ($P < 0.001$) and between relatives and controls ($P = 0.016$) was statistically significant. Increased consumption of red meat [odds ratio (OR) 0.69 95% CI 0.2, 2.34 for cases versus relatives and odds ratio (OR) 1.84 95% CI 0.41, 8.36 for patients versus controls] was not independently associated with ($P = 0.516$) an increased risk for colorectal cancer. Similarly smoking [odds ratio (OR) 1.1 95% CI 0.28, 4.28 for patients versus relatives and odds ratio (OR) 0.4 95% CI 0.09, 1.67 for patients versus controls] was not ($P = 0.43$) independently associated with increase in risk for colorectal cancer. NAT2-imputed phenotype might modify colorectal cancer risk.

Title: An Unusal Case of Hyponatraemia

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INTRODUCTION

Hyponatraemia is the most prevalent electrolyte abnormality in hospitalised children. It is defined as a plasma sodium concentration <130 mmol/L. Common causes include; diarrhoea, vomiting, diuretics, syndrome of inappropriate ADH secretion (SIADH) and inadequate water excretion.

TREATMENT

MH presented in A and E on the 5/8/2005 with bone pain. Stage four neuroblastoma was diagnosed. Chemotherapy was initiated on 12/8/05 to shrink the tumour prior to surgical removal. The chemotherapy protocol consisted of vincristine, cisplatin and carboplatin. Over the 70 day course of chemotherapy, plasma sodium level fell to 124 mmol/L and plasma osmolality fell to 268 mmol/kg. Urine sodium increased to 162 mmol/L and urine osmolality increased to 401 mmol/kg as plasma sodium fell. Frusemide administration was stopped, and SIADH (due to vincristine chemotherapy) was ruled out. IV infusion was increased from 0.45 % saline to 0.9 % saline giving an increase of 6mmol/kg body weight of sodium/day. After the 70 days chemotherapy, the tumour was removed and her electrolyte values returned relative to normal post operatively.

CONCLUSION

It was concluded that the electrolyte imbalance and renal sodium loss seen in this patient were a result of renal tubular dysfunction secondary to nephrotoxic chemotherapy agents used to treat the neuroblastoma.

Title: Severe Hypertriglyceridaemia presenting with altered mental state and acute pancreatitis at 2 years of age.

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INTRODUCTION

Type 1 hyperlipidaemia, as a result of apo C-II or lipoprotein lipase (LpL) deficiency, is a rare autosomal recessive disorder resulting in the accumulation of chylomicrons in plasma and subsequent severe fasting hypertriglyceridaemia. Apo C-II, a peripheral apoprotein of chylomicrons, VLDLs and IDLs, activates LpL to hydrolyze triglycerides to release free fatty acids for cellular absorption. Clinical features are variable and include eruptive xanthomas, lipaemia retinalis, hepatosplenomegaly, and an increased risk of acute pancreatitis.

CLINICAL PRESENTATION

A 2yr old boy, the son of consanguineous parents, presented with drowsiness, decreased consciousness and poor feeding. A family history of Glutaric Aciduria Type 1 (GA1) necessitated the investigation of a metabolic disease as a likely cause. A brain CT scan revealed no abnormality.

LABORATORY FINDINGS

Initial venepuncture showed "milky" blood that was visibly grossly lipaemic. In view of this, a full renal/liver/bone workup was requested along with cholesterol, triglyceride and amylase levels. Biochemical analysis showed a plasma triglyceride level of 60.4 mmol/l (0.5-2.0), a cholesterol level of 15.8 mmol/l (2.5-5.5) and an amylase level of 293 U/l (0-100). Following these findings, samples were sent to a referral laboratory for lipoprotein lipase and apo-CII levels. The lipoprotein lipase level of 1.9 umol FFA/ml/hr (Type 1 hyperlipidaemia <0.2 umol FFA/ml/hr) was deemed borderline low but not absent. Apo C-II was normal. This child has impaired LpL but not a complete deficiency.

OUTCOME

The acute pancreatitis was treated and the patient placed on a fat restricted diet. Within 3 days the plasma triglyceride level fell to 4.8 mmol/l which, although far from normal, is deemed under good control. The chance of a reoccurrence of a clinical episode will be kept to a minimum as long as dietary advice is adhered to. However, low LpL activity is often not sufficient in itself to lead to very elevated levels of triglyceride and may just be a contributory cause.



Notes