CONTENTS

WELCOME MESSAGES

Welcome Message From The Organising Committee

On behalf of the organising committee, we welcome you to the second annual scientific meeting of the Australia and New Zealand Child Neurology Society.

Our focus has been on cutting edge science as it relates to a range of neurology topics providing a high quality teaching experience for members and trainees of the ANZCNS.

This year the program includes speakers with expertise in the following areas:-

- Neuromuscular disorders
- Autoimmune CNS disorders
- Epilepsy including encephalopathies, genetics and classification
- Neuro-metabolic disorders
- Headache

In addition there will be platform presentations for members and trainees of the ANZCNS to present their research and cases for discussion.

We hope you enjoy your stay at Q Station Sydney Harbour National Park Manly. This site is well worth exploring and encompasses the colour, history, life and the cultural significance of Sydney harbour and the wider region.

Hugo Sampaio
Co-Chair, Organising Committee

Michael Cardamone
Co-Chair, Organising Committee

Welcome Message From The Australia And New Zealand Child Neurology Society

On behalf of the ANZCNS, I would like to invite you to our 2013 Annual Scientific Meeting. Michael Cardamone, Hugo Sampaio and Kate Riney have worked hard to arrange an exciting meeting at the Q station in Manly. This historic venue is located in a beautiful site at Sydney North's Head, and offers a spectacular venue, a range of activities and is only a short distance from Manly and a ferry ride from Sydney City. This is the first meeting of our group since our very successful international meeting last year, and ensures that the momentum within our organization to continue to advance Paediatric Neurology in Australia and New Zealand is maintained.

Richard Webster
Chief Executive Officer, Australia and New Zealand Child Neurology Society

About Australia and New Zealand Child Neurology Society

The Australia and New Zealand Child Neurology Society (ANZCNS) is a collaborative group of approximately 90 Paediatric Neurologists and Paediatric Neurology Trainees from all over Australia and New Zealand, the majority of whom attend the annual scientific meeting. The organisation aims to promote the best possible care for children with neurological disease by fostering education and training of those who care for children with neurological diseases, advancing neuro-paediatric research and promoting improved standards of care for children with neurological disease. More information about ANZCNS is available on the ANZCNS website: www.anzcns.org.au

COMMITTEES

Organizing Committee

H Sampaio (Co-Chair)
M Cardamone (Co-Chair)
K Riney
R Webster

Abstract Review Committee

K Riney
A Cairns
M Ryan
R Webster
L Nagarajan
H Sampaio
M Cardamone

Poster and Platform Prize Judges

B Appleton
G Wise
A Bye

GENERAL CONFERENCE INFORMATION

Secretariat Office

Members of the Committee can be contacted at the registration desk in the breakout room adjacent to the lecture theatre set up in the 'old hospital'. For urgent queries during the conference please contact Hugo Sampaio on 0415 672 583 or Michael Cardamone on 0412 707 729.

For queries arising after the congress, please contact:

Australia and New Zealand Child Neurology Society
PO Box 8446, Woolloongabba, QLD 4102, Australia

f: +61 7 31631722
e: admin@anzcns.org.au
t: +61 7 31631697

Conference Venue

On the edge of Sydney Harbour at Manly, just 30 minutes from the centre of Sydney and surrounded by bushland and stunning views of the harbour and Manly Cove. Q Station is the former Quarantine Station for Sydney and is preserved within 30 hectares of the Sydney Harbour National Park. Carefully restored and sympathetically adapted, Q Station now provides contemporary accommodation, conference facilities, restaurants, a Visitors Centre and Museum and a popular program of tours and activities.

Getting to and from the Venue

Address:
Q Station, 1 North Head Scenic Drive, Manly NSW 2095

Ferry:
From Circular Quay; the fare is $14.50 per journey.
Timetables are available at www.manlyfastferry.com.au

Bus:
Route 135, time table information available at www.131500.com.au

Taxi:
Taking 35 minutes from the domestic airport terminal, the fare is approximately $70.

Registration Desk

The registration desk is located in the breakout room (H1A) in the old hospital precinct, adjacent to the meeting room (H1B). Congress bags and name badges can be collected from this point. Delegates must provide government-issued photo identification (eg passport, driver's licence) along with a printed copy of their registration confirmation to facilitate registration. Please note that name badges must be clearly displayed at all times.

Registration Entitlements

- Entry to all conference sessions and trade exhibition area
- Morning tea, lunch, afternoon tea
- Congress satchel and delegate satchel material
- Printed program

Speakers' Information

Speakers must submit their final presentation to one of the conference organisers **at least 4 hours prior to their session start time**.

Exhibition

A trade exhibition is held in conjunction with the 2nd ANZCNS ASM. This is an integral part of the event and allows delegates the opportunity to be updated on the latest developments in products and services in the field of child neurology. The exhibition area is located in in the breakout room.

Posters

Posters are exhibited in the breakout room. Poster presenters are asked to stand by their posters during the lunch break on Saturday the 4th of May 2013.

Posters should be set up by 11am on Friday the 3rd of May and should be removed by 3pm on Sunday the 5th of May.

Continuing Medical Education

Fellows and trainees of the Royal Australasian College of Physicians can apply for one credit for each hour attended of the academic program of the conference.

Certificate of Attendance

A certificate of attendance is available for all delegates for collection from the registration desk on the last day of the conference.

Catering

Lunches and morning and afternoon teas are served in the breakout room. Any delegates with particular catering needs who have not noted these on their registration form should contact the organisers at least 2 weeks prior to the start of the conference (by email admin@anzcns.org.au).

Dress Code

The 2nd ANZCNS ASM promotes casual business attire for the duration of the conference.

Mobile/cell phones

Mobile/cell phones **must** be turned off or to vibrate mode during all sessions so as not to disturb speakers or other delegates. Pagers should be on vibrate mode.

Community and Consumer Delegates

The 2nd ANZCNS ASM is primarily for health professionals. Community and consumer support groups have been welcomed to 2nd ANZCNS ASM to allow partnerships with health professionals

towards a common goal. Such delegates should understand that the presentations will contain medical jargon and may contain information and images that some might find distressing. Questions from the open floor during sessions are invited primarily from health professionals.

Photography

The 2nd ANZCNS ASM strictly prohibits all photography (flash, digital, or otherwise), audio and/or videotaping during the congress except by authorised photographers. There will official photographers who will be capturing candid photos of the conference. These photographs will be used in congress communications. In registering and attending this conference you accept that your likeness may be taken in the form of photographs taken by photographers approved by Australia and New Zealand Child Neurology Society for activities related to this and future conferences (including but not limited to: use within newsletters, presentations or other media that recounts the events that occurred during this conference and/or in the promotion of future conferences). Delegates should inform the Australia and New Zealand Child Neurology Society (by email or in writing) in advance of the congress week if they do not provide permission for this. Delegates may also provide this information at the Registration Desk.

Liability and Insurance

The Australia and New Zealand Child Neurology Society will not accept any liability for personal injury or loss/damage to property/belongings of participants or accompanying persons, either during or following the conference or their stay. It is recommended that delegates arrange their own personal health, accident and travel insurance for themselves and their families.

SOCIAL EVENTS

Conference Dinner

The Conference Dinner will be held in the A20 dining room at Q Stations, on Saturday the 4th of May at 19:00 hours. Enjoy the opportunity to meet with colleagues and friends from Australia, New Zealand and internationally. The dress code is casual evening attire. Dinner includes a three course meal and beverages.

Tickets are AUD$110. Tickets must be purchased in advance of the conference.

Suggestions for activities

Q Station offers numerous activities to encourage delegates to explore its splendid surroundings and to learn about the heritage of the site. Examples of offerings are included below, more details can be found at www.qstation.com.au or by contacting one of the conference organisers.

- 40 Days Tour @ $35 per person
- Ghost tours from $44 per person
- Wharf wander tour from $15 per person
- Quarantine Station Story from $35 per person – 2 hours
- Nature Walk from $35.00 per person – 2 hours

SPONSORS

The Australia and New Zealand Child Neurology Society wish to extend their thanks to our major sponsors who have supported this event:

MAJOR SPONSORS

NOVARTIS

ucb

EXHIBITORS

Aurora Bioscience Pty Ltd

Genzyme, A Sanofi Company

Batten Disease Support and Research Association

FRIDAY 3RD MAY

Time	Event	Speaker	Venue
08.30	ANZCNS Board meeting		H1B
08:30	**Trainees breakfast**		Manly
10:00	ANZCNS Special Interest Group – Research Interest Group Meeting		H1B
11:00	**Arrival tea and coffee at venue**		H1A
11:15	ANZCNS Annual Trainee Lecture	Robert Ouvrier	H1B
12:00	**Lunch and registration**		H1A
	Afternoon Session (Chair: Monique Ryan)		
13:00	Newborn epileptic encephalopathies	Rani Sachdev	H1B
13:30	Neonatal seizures: EEG and clinical features	Lakshmi Nagarajan	H1B
14:00	Comparison of pathological and electroclinical characteristics in an adult and paediatric temporal lobe epilepsy surgical cohort	Alexandra Johnson / Annie Bye	H1B
14:30	Neuroimmunology update: autoantibodies in CNS disease	Russell Dale	H1B
15:00	Inborn errors of cobalamin metabolism	Michelle Lipke	H1B
15:30	**Afternoon tea**		H1A
	Afternoon Platform Session (Chair: Lakshmi Nagarajan)		
15:45	Platform Presentations		H1B
17:00	ANZCNS members meeting		H1B
18:00	**Close**		

11:00 **ANZCNS ANNUAL TRAINEE LECTURE** **H1B**
Robert Ouvrier

Professor Robert Ouvrier graduated BSc (Med) with Honours in 1961, MBBS with Honours in 1964, and MD in 1986, at the University of Sydney. He was appointed Head of the T.Y. Nelson Department of Neurology and Neurosurgery in 1978 and was the Foundation Head of the Institute for Neuromuscular Research at The Children's Hospital at Westmead and is a Senior Staff Specialist in this Hospital. Professor Ouvrier was appointed a Clinical Professor in the Department of Paediatrics at the University of Sydney in 1999. He became the Petre Foundation Professor of Paediatric Neurology in 2001 and Emeritus Professor in 2011. He was President of the International Child Neurology Association from 2006-2010. He is the author of two books, thirty book chapters and an author or co-author of over one hundred and fifty scientific articles on paediatric neurology. He has been an invited overseas lecturer on more than 50 occasions in the field of child neurology.

In keeping with ANZCNS's commitment to improving training and education for trainees in Paediatric Neurology, each year at the Annual Scientific Meeting there will be a dedicated interactive lecture for trainees provided by a Senior Paediatric Neurologist on a relevant area in Paediatric Neurology. This year, ANZCNS is delighted to present Professor Ouvrier, who will discuss the important topic of the anatomical and physiological basis of normal and abnormal nerve conduction studies. All trainees attending the scientific meeting are asked to attend this lecture.

13:00 **NEWBORN EPILEPTIC ENCEPHALOPATHIES** **H1B**
Rani Sachdev

Dr Rani Sachdev is a clinical geneticist with a special interest in epilepsy genetics. Her experience at the Radcliffe Hospital in Oxford as well as appointments at Royal Prince Alfred, Liverpool and Sydney Children's Hospitals in Sydney have inspired her to develop a knowledge in this field.

Genetic causes of neonatal/infantile onset epileptic encephalopathies are rapidly becoming more evident. This session will summarize recent updates on these specific genes and associated clinical syndromes and in addition will briefly discuss the benefits and pitfalls associated with specific gene testing.

13:30 **NEONATAL SEIZURES: EEG AND CLINICAL FEATURES** **H1B**
Lakshmi Nagarajan

Professor Lakshmi Nagarajan is a paediatric neurologist/epileptologist at Princess Margaret Hospital for Children in Perth, where she is Head of the Department of Neurology and is a Clinical Professor at the University of Western Australia. Professor Nagarajan chairs the Education and Research Committee of the Epilepsy Society of Australia and is a Director of the Australia and New Zealand Child Neurology Society. Lakshmi's research interests include neonatal seizures, epilepsy and neurophysiology.

Neonatal seizures are a challenge to diagnose and manage. Under-recognition and over reporting of neonatal seizures is known to occur. Electrographic seizures without any clinical correlates occur frequently in the newborn. Clinically diagnosed 'seizures' include many paroxysmal phenomena that do not have surface EEG correlates. In this presentation, Professor Nagarajan will discuss the clinical semiology of seizures with EEG correlates and the EEG features of electroclinical and electrographic seizures in neonates.

14:00 **COMPARISON OF PATHOLOGICAL AND ELECTROCLINICAL CHARACTERISTICS IN AN ADULT AND PAEDIATRIC TEMPORAL LOBE EPILEPSY SURGICAL COHORT** **H1B**

Annie Bye & Alexandra Johnson

Associate Professor Annie Bye is a senior paediatric neurologist and Head of Department. Her area of interest is epilepsy at Sydney Children's Hospital. She is supervising the Masters of Dr Alexandra Johnson.

Dr Alexandra Johnson is a paediatric neurologist and is presently undertaking a Masters of Medicine (Research). She is also in private practice in paediatric neurology.

Background: There is limited data on pathological substrates and electroclinical syndromes comparing adults and children undergoing temporal lobe epilepsy (TLE) surgery.

Objectives: The study aim was to compare children and adults' pathologies, clinical, radiological and electrographic correlates in a TLE surgical cohort.

Methods: Children (n=26) and adults (n=47) were recruited from TLE surgery patients operated between 2002-2011 at our campus. Blinded review occurred of 1) Pathology and controls by neuropathologist, and 2) MRIs by neurologist/neuroradiologist. EEG, clinical data and outcome established through notes review and/or patient contact.

Results: The commonest pathologies were hippocampal sclerosis (HS) (adults n=37) and tumour (children n=17).

Paediatric HS was associated with febrile status (n=4/7,p=0.004). Preceding intracranial infection/trauma appeared exclusively in adult HS (n=15). Multi-regional neuropsychological deficit was associated with adult HS (n=20,p=0.045). Paediatric tumour had the highest seizure frequency (mean=44.5/month,p=0.011).

Generalised seizures were commonest in adults (n=40,p<0.0005), and negatively associated with postoperative seizure freedom (p=0.007). Post-operatively, paediatric TLE had increased seizure freedom (n=16,p=0.01) and medication cessation (n=10,p<0.0005).

Conclusion: Adult and paediatric TLE surgical patients are significantly different regarding pathology, clinical presentation and outcome. More adults with intractable TLE have generalised seizures pre-operatively. Post-operatively, paediatric TLE has improved outcome with higher rates of seizure freedom and medication cessation.

14:30 **NEUROIMMUNOLOGY UPDATE: AUTOANTIBODIES IN CNS DISEASE** **H1B**
Russell Dale

Associate Professor Russell Dale is a clinical academic and neurologist with interest in paediatric neuroimmunology and movement disorders. He runs the movement disorder service (with Dr Paddy Grattan-Smith), the Tourette service and provides neuroimmunology opinion. He is postgraduate coordinator and oversees the progress of over 100 postgraduate research students at the Children's Hospital at Westmead.

Autoantibodies are an increasingly utilised biomarker in acquired brain and spine disease in children. Some of the autoantibodies are pathogenic, whereas for other autoantibodies the pathogenicity is unproven. The recent paradigms in the field state that autoantibodies that are pathogenic bind to the cell surface of neurones and the extracellular domain of receptors and synaptic proteins involved in neurotransmission.

In this talk we will cover some of the autoimmune CNS conditions, in which the autoantibody is proven or very likely to be pathogenic, focussing on NMDAR encephalitis and Neuromyelitis optica spectrum.

In addition we will cover autoantibodies which are not yet shown to be pathogenic, focussing on VGKC complex antibodies in limbic encephalitis and autoimmune epilepsy, and Dopamine-2 receptor antibodies in autoimmune movement disorders.

In addition we will cover some challenging topics such as:

- When do we use second line therapy in autoimmune brain disease?
- Should we treat all autoimmune CNS disease in the same way?
- What should we do with antibody negative patients when an autoimmune CNS disease is still suspected?

15:00 **INBORN ERRORS OF COBALAMIN METABOLISM** **H1B**
Michelle Lipke

Dr Michelle Lipke is a metabolic physician based at the Sydney Children's Hospital in Randwick. She trained in metabolic medicine in Queensland, South Australia and Victoria.

The metabolism of Vitamin B12 involves complex mechanisms for absorption, transport and intracellular conversions. This presentation focuses on the clinical features, as well as diagnostic and management approaches to patients with inborn errors of cobalamin metabolism.

15:45-17:00 **PLATFORM ABSTRACTS** **H1B**

15:45 **Herpes simplex encephalitis relapse with chorea is associated with autoantibodies to NMDA Receptor or Dopamine-2 receptor**

Shekeeb Mohammad, Children's Hospital Westmead

Movement disorder relapses after Herpes Simplex Virus 1 (HSV1) encephalitis have been hypothesised to be secondary to post-viral autoimmunity. Recently a proportion of patients with HSV1 encephalitis (HSE) were shown to produce autoantibodies against N-Methyl-D-aspartate receptor (NMDAR)[1]. We have recently shown that NMDAR antibody negative patients with autoimmune encephalitis complicated by movement disorders can instead have autoantibodies that bind to the extracellular domain of the dopamine-2 receptor (D2R)[2].

Methods: We measured autoantibodies against NMDAR and Dopamine-2 receptor (D2R) expressed at the cell surface in the stored acute serum of nine children with HSE, three of whom had a relapsing course with chorea.

Results: The three patients with chorea had elevated autoantibodies against NMDAR (n=1), D2R (n=1) or both (n=1), whereas patients without chorea were negative (n=6). The prospectively identified patient with chorea and NMDAR autoantibodies improved after early treatment with steroids, intravenous immunoglobulin and cyclophosphamide with reduction in serum NMDAR antibody titres and decreased binding to hippocampal neurons.

Conclusions: These autoantibody findings lend support to the autoimmune hypothesis and the early use of immune suppression in post HSE chorea.

References:

1. Pruss H, Finke C, Holtje M, et al. N-methyl-D-aspartate receptor antibodies in herpes simplex encephalitis. Ann Neurol 2012;72(6):902-911.
2. Dale RC, Merheb V, Pillai S, et al. Antibodies to surface dopamine-2 receptor in autoimmune movement and psychiatric disorders. Brain 2012;135(Pt 11):3453-3468

16:00 **ICU management of non-intubated children with severe anti-NMDAR encephalitis: an interdisciplinary challenge - lessons learned**

Christina Miteff, John Hunter Children's Hospital

Background: Anti-NMDAR encephalitis was first described by Dalmau in 2007. The acute presentation typically involves psychosis, seizures, dyskinesias, as well as autonomic instability. ICU admission is often required for dyskinesias/agitation and ventilator support.

Case report: We present our experience with a 12 year old boy and the unique problems associated with prolonged ICU management once he was extubated. We found very little literature to help guide us. Advice from several sources was often anecdotal. Our patient required

meticulous management of the dyskinesias, paroxysmal sympathetic hyperactivity and cardiac dysrhythmias. Another major challenge was adjustment to the constant change in clinical state on lifting sedation. A crucial challenge was the need to balance expectations from parents, ICU nursing and medical staff and the neurology team. In particular, we found that parental input regarding medication effects, side-effects, and treatment protocols was essential. We acknowledge the value of parental networks including "Facebook".

Conclusion: ICU management of non-intubated anti-NMDAR encephalitis demands "thinking outside the box". Parental involvement was essential and communication between parents and the medical teams involved required flexibility, creativity and most of all humility.

16:15 **Risk of Multiple Sclerosis after a first demyelinating syndrome: clinical, radiological features and application of McDonald 2010 MRI criteria**

Esther Tantsis, Children's Hospital Westmead

Background: The risk of multiple sclerosis (MS) is dependent upon multiple variables including geographical location. There is increasing interest in the early recognition and treatment of MS in children.

Methods: Using univariate and multivariate analysis we determined the clinical and radiological features that were predictive of MS in 88 children from New South Wales, Australia with a first acute demyelinating syndrome (ADS) who were followed for a minimum of one year.

Results: After a mean follow-up of 5.2 years, 13/88 (15%) of children had MS. Using multivariate analysis, preceding infection was protective of MS and corpus callosal lesions, the combined presence of both well and poorly demarcated lesions and contrast enhancing lesions were predictive of MS. The sensitivity and specificity of the respective radiological criteria were McDonald 2005 (69%, 68%), McDonald 2010 (58%, 95%), KIDMUS (8%, 100%), Callen (69%, 85%), and Verhey (62%, 84%). When McDonald 2010 criteria were applied to baseline and serial scans, the sensitivity and specificity was 91% and 93%.

Conclusion: Despite the long follow-up the risk of MS appears lower than previously reported. The McDonald 2010 criteria performed well although the dissemination in time criteria on baseline scans is difficult to apply to children with encephalopathy.

16:30 **Fatal pediatric case of Australian Bat Lyssavirus (ABL) infection**

Sophie Calvert, Mater Children's Hospital

The Australian Bat Lyssavirus (ABL) was first recognized in 1996. Both human cases previously reported were fatal. A previously healthy, fully immunised 8 year old boy was admitted to hospital 8 weeks after an unwitnessed encounter with a bat. He presented with a three day history of fever, sore throat, abdominal pain, and worsening agitation and combativeness. Due to increasing pain, agitation and dysphagia he was intubated and sedated, and transferred to paediatric intensive

care. Examination while sedated revealed significant dysautonomia with tachycardia, hypertension, and intermittent arrhythmias on stimulation. When sedation was lifted the patient became agitated with facial grimacing and muscle spasms but appeared to maintain awareness and at times was lucid enough to request re-sedation. Initial testing was negative for Lyssavirus, and several other differentials were investigated, including tetanus and ciguatoxin. Repeat testing (day 10) demonstrated positive ABL PCR on saliva and CSF samples. Neuroimaging was initially normal but serial neuroimaging showed progressive changes in the basal ganglia, thalami, hippocampi, temporal lobes, midbrain, cerebral peduncles, periaqueductal grey matter, pons and cerebellum. Neurological deterioration, associated with fixed and dilated pupils and an isoelectric EEG, preceded death on day 28 of hospital admission.

Conclusion: This case report describes the first pediatric case of ABL infection. Increased public awareness of this fatal disease and its association with native bats is important as effective post-exposure prophylaxis is available.

16:45 **The pseudo-poliomyelitis of the 21st century**
Hooi Ling Teoh, Sydney Children's Hospital

It has been 12 years since enterovirus 71 haunted the hallways of our hospital, with 18 of 200 children affected experiencing neurologic complications. Between January 2013 and March 2013, 30 children presented with neurologic symptoms and enterovirus positivity on faeces, throat swab, serum or CSF. 14 out of the 30 were genotyped (the remainder pending at time of submission) and all were found to have enterovirus 71. Of the 18 patients who had an MRI scan, two thirds showed an abnormality with increased T2 signal intensity in the brainstem +/- spinal cord involvement seen. Symptoms of these patients were varied and included: neurogenic pulmonary oedema with quadriparesis, seizures, myoclonic jerks (almost invariable), monoplegia, unilateral cranial nerve 6 palsy, generalised weakness, irritability and neurogenic bladder. Treatment was also variable with 3 needing full cardio-respiratory support with intravenous immunoglobulin (IVIG) and high dose methylprednisolone, 4 receiving IVIG and high dose methylprednisolone, 4 receiving only high dose methylprednisolone and 4 receiving only IVIG and 15 receiving no special treatment. 29 children improved in their clinical course. All patients presenting with limb weakness, although improved, continue to have residual weakness at follow up in the presence of a normal MRI, regardless of treatment. Follow up is on-going.

SATURDAY 4TH MAY

Time	Event	Speaker	Venue
	Early Morning Session (Chair: Richard Webster)		
09:00	**Keynote Lecture** Building on our inheritance: The revolution in genome diagnostics	Michael Buckley	H1B
10:00	Massively parallel sequencing massively alters clinical practice	Ingrid Scheffer	H1B
10:40	**Morning tea**		H1A
	Late Morning Session (Chair: Anita Cairns)		
11:00	Management of chronic headache	Alessandro Zagami	H1B
11:30	Mitochondrial disorders update	David Thorburn	H1B
12:10	Unravelling the X chromosome: a road map of X linked intellectual disability	Michael Field	H1B
12:40	**Lunch**		H1A
	Afternoon Session (Chair: Kate Riney)		
13:30	Psychotropic medication in neurology	Brett McDermott	H1B
14:10	Learning disabilities in NF1	Kathryn North	H1B
14:40	Emerging therapies in NF1	Simone Ardern-Holmes	H1B
15:00	Emerging therapies in TS	John Lawson	H1B
15:20	Neurological manifestations of hyperekplexia	Grahame Wise with introduction by Annie Bye	H1B
15:40	**Afternoon tea followed by Q Station Activities**		H1A
19:00	**Conference dinner**		A20

09:00 **BUILDING ON OUR INHERITANCE: THE REVOLUTION IN GENOME DIAGNOSTICS** **H1B**

Michael Buckley

Dr Michael Buckley is a clinical molecular geneticist and director of the genetics laboratories on the Randwick hospitals campus in Sydney with a conjoint appointment as Associate Professor in the UNSW School of Medical Sciences. He is a graduate of the University of Auckland School of Medicine and Monash University, Melbourne with a PhD in genetic pathology. From 1991 he held an NHMRC Australian Postdoctoral Fellowship at the Garvan Institute, Sydney before taking up this current position as a staff specialist pathologist in the mid-1990s. Between 2000 and 2008 Dr Buckley was the Registrar of the RCPA Board of Censors and Chief Examiner in genetics for the RCPA and molecular genetics the HGSA. From 2008-2011 he was awarded a Marie Curie International Fellowship from the EU Science Directorate at the Dept of Human Genetics of Radboud University Nijmegen Medical Centre in the Netherlands to work on projects relating to the clinical implementation of next generation sequencing. His current interests include disease gene identification studies for paediatric disorders.

Genome diagnostics is the field that unites classical cytogenetics and molecular diagnostics. The introduction of genomics will radically improve the scope and cost of providing laboratory diagnoses to paediatricians. The successful implementation of genomic testing will require clinician input through-out the process, from diagnosis and test design, through to data interpretation.

This talk will outline the technological changes which have enabled genomic diagnoses, and propose the development of a multidisciplinary team approach for patient diagnosis and management.

10:00 **GENETICS OF EPILEPSY** **H1B**

Ingrid Scheffer

Professor Ingrid Scheffer is a paediatric neurologist and epileptologist at the Florey Institute, University of Melbourne and at the Austin Health and Royal Children's Hospitals, Melbourne. Her work together with collaborators has led the field of epilepsy genetics research over the last 22 years. Her research interests include the genetics of epilepsy, epilepsy syndrome classification, and genetics of autism spectrum disorders and speech and language disorders.

With the advent of whole-exome sequencing and next generation sequencing of multigene panels in epilepsy, the genetic architecture of the epileptic encephalopathies is changing rapidly. Many new genes are being identified and this will lead to insights into specific genetic epileptic encephalopathies. Several recent studies will be presented, including whole-exome sequencing in a large cohort of patients with Lennox-Gastaut syndrome and infantile spasms and the results of multigene sequencing in 500 patients with epileptic encephalopathies defining two important new epilepsy genes. In

addition, a gene for focal epilepsy that relates to less clear-cut familial cases will be discussed. The insights from these studies suggest that genetic testing will now result in molecular determinants for at least one third of all patients with epileptic encephalopathies and will cause a major paradigm shift in approaches to testing focal epilepsies.

11:00 **MANAGEMENT OF CHRONIC HEADACHE** **H1B**

Alessandro Zagami

Associate Professor Alessandro Zagami is one of Australia's leading clinician scientists in headache. He is a founding member of the Australian Headache Society, has been a member of IHS since 1988 and is a member of the American Headache Society. He sat on the Headache Classification Subcommittee on Cranial Neuralgias contributing to the ICDH-II. His research is funded by NHMRC and the Australian Brain Foundation.

Chronic daily headache (CDH) is purely a descriptive term and is defined as a headache occurring more than 15 days in a month. Worldwide it has a prevalence of about 4%. The term chronic means different things with different headache forms. These include chronic tension type headache, chronic cluster headache, chronic paroxysmal hemicrania and, chronic migraine (CM) which is believed to make up 50% of CDH. Previous terms for CM included transformed migraine and it was only in 2004 that a definition of CM was established in the second edition of the International Classification of Headaches Disorders. These proposed criteria have been revised since. There are other headaches that are not labelled as chronic even though they clearly are such as hemicrania continua, new daily persistent headache and the trigeminal autonomic cephalalgias. Medication overuse headache is another common cause of CDH. Medication overuse may contribute to the development of CM. Some patients with CM however, do not overuse medications and other possible risk factors will be discussed. Obviously the treatment of the various causes of CDH differs and only some will discussed. A particularly important aspect of treatment will be to identify patients at risk of developing CM so that this can be prevented.

11:30 **MITOCHONDRIAL DISORDERS UPDATE** **H1B**

David Thorburn

Professor David Thorburn is an NHMRC Principal Research Fellow and Director of the Genetic Disorders Theme at the Murdoch Childrens Research Institute. His laboratory acts as the Australasian referral centre for children suspected of mitochondrial disease. They have diagnosed over 500 patients with mitochondrial disease and are using Massively Parallel DNA sequencing to improve diagnosis.

Mitochondrial Oxidative Phosphorylation (OXPHOS) disorders affect at least 1 in 5000 births and pose great challenges in diagnosis and treatment. OXPHOS disorders show enormous clinical and genetic heterogeneity. OXPHOS disorders can be caused by mutations in

the maternally inherited mitochondrial DNA (mtDNA) or in nuclear genes resulting in autosomal recessive, autosomal dominant or X-linked inheritance. Over 140 OXPHOS "disease" genes are known and perhaps another 100 await identification. Known nuclear disease genes encode OXPHOS subunits plus proteins required for OXPHOS biogenesis, mtDNA maintenance or expression and synthesis of components of the mitochondrial inner membrane. Currently, most patients with OXPHOS disorders do not have a molecular diagnosis. Genetic diagnosis is challenging as sequential analysis of candidate genes can be inefficient and expensive. OXPHOS disorders are one of the most obvious groups of genetic diseases that could benefit from the application of massively parallel sequencing (MPS). We recently described MitoExome analysis for targeted DNA capture and MPS of over 1000 genes encoding the known mitochondrial proteome, which offers a powerful approach to molecular diagnosis of these disorders. However, high quality clinical and laboratory investigations, particularly respiratory chain enzymes, remain very important in interpreting and validating MPS results.

12:10 **UNRAVELLING THE X CHROMOSOME: A ROAD MAP OF X LINKED INTELLECTUAL DISABILITY** **H1B**

Michael Field

Dr Michael Field is a paediatric clinical geneticist who is acting director of the Genetics of Learning Disability Service (GOLD). The last ten years has seen an explosion in our knowledge about the genetic cause of intellectual disability with the patient cohort collected by the GOLD Service being a core resource for many of these discoveries.

It is estimated that 10% of intellectual disability is X linked. The ability to collect large families with both affected and unaffected members has made this pattern of intellectual disability ideal for early genetic research. The fragile site associated with fragile X syndrome was first described by Lubs in 1969 but it took another 22 years for the FMR1 gene to be identified. Today there are well over a hundred genes on the X chromosome implicated in the cause of intellectual disability with the majority being identified in the last 10 years. The advent of massively parallel sequencing will soon bring this knowledge into routine clinical practice.

Identification of the cause of familial intellectual disability allows restoration of reproductive confidence or access to appropriate prenatal testing. Improved knowledge about gene function will allow therapeutic intervention with targeted treatment trials in fragile X syndrome already underway.

This talk will include a brief description of the rapid advances in our knowledge about the cause of X-linked intellectual disability and the role that the genetics of learning disability cohort played in these discoveries, discuss the neurological features and phenotypes seen in association with mutations in ARX and CASK, and outline directions for future research into intellectual disability.

13:30 **PSYCHOTROPIC MEDICATIONS IN NEUROLOGY** **H1B**

Brett McDermott

Professor Brett McDermott is an Australian/UK trained child and adolescent psychiatrist. Current appointments: Executive Director (Mater Child and Youth Mental Health Service), Professorial Fellow (Mater Medical Research Institute), By-Fellow (Churchill College, Cambridge University) and director of Beyondblue. His interests include child and adolescent depression, post-traumatic mental health, and CAHMS models of care.

Psychotrophic medications generally include antidepressant, antianxiety, antipsychotic and stimulant medication. Used less frequently are mood stabilisers and a diverse range of medications such as melatonin. Psychotrophic medications are used in neurology when the patient experiences a co-morbid mental health presentation e.g. depression or when there is significant emotional or behavioural disturbance and non-pharmacological measures have not proven efficacious. The evidence base for using these medications with young people (e.g. the 2012 NHMRC-Beyondblue clinical practice guidelines for adolescent depression) will be reviewed. So too side effects including recent evidence of metabolic syndrome following the use of second-generation antipsychotics in children. The talk will conclude with more controversial issues such as paediatric bipolar disorder and off-label use of psychotrophic drugs.

14:10 **LEARNING DISABILITIES IN NF1** **H1B**

Kathryn North

Professor Kathryn North is Director of the Murdoch Children's Research Institute and the David Danks Professor of Child Health Research at the University of Melbourne.

Professor North established the first Australian Neurofibromatosis Clinic in 1991. Over the past 20 years, Professor North and her research team have focused on defining the cognitive phenotype associated with NF1, and developed guidelines for the management of learning disabilities in NF1 for the US Children's Tumor Foundation (2008). Professor North is a Principle Investigator in the trial of Lovostatin for the treatment of cognitive deficits in NF1 as part of the NF Clinical Trials Consortium.

Cognitive deficits and academic learning difficulties are the most common neurological 'complication' of NF1 in childhood and can be responsible for significant lifetime morbidity; indeed we encounter some form of cognitive impairment in up to 70% of children in our clinic. We now have an accurate understanding of the cognitive phenotype in school aged children with NF1 and the focus of current research is on providing effective and early interventions. In addition there is now a potential for effective and specific pharmacological therapies, based on reversal of cognitive deficits in the Nf1 mouse model using ras inhibitors including Lovostatin.

Intellectual function is static in individuals with NF1 over time – from primary school age into young adulthood, and our current studies are focusing on how early we can identify specific deficits the preschool age group. While the cognitive profile of patients demonstrates a range of deficits that are much more common in NF1, the specific features vary markedly between individual patients. Common features include a lowering of full scale IQ (37% of children with NF1 have full scale IQ more than 1 SD below the population mean); problems with visuospatial tasks, deficits in executive function that include problems with planning, forming abstract concepts, and u ilizing feedback, and difficulties with sustaining and switching their attention. Approximately 35-40% have ADHD (using DSM-IV criteria), and the presence of ADHD is the major contributor to the development of specific learning disability and poor social skills in children with NF1. Reading difficulties are also much more common in children than previously recognized. In this presentation I will provide an overview of the NF1 cognitive phenotype, studies focussed on early identification and the natural history of cognitive deficits and the issues that need to be considered in the conduct of phase II/III clinical trials.

14:40 **EMERGING THERAPIES IN NF1** **H1B**

Simone Ardern-Holmes

Dr Simone Ardern-Holmes is a paediatric neurologist at The Children's Hospital Westmead campus of The Sydney Children's Hospitals Network. Her interest and expertise includes the management of the neurologic complications of neurocutaneous disorders, specifically Neurofibromatosis Types 1 and 2.

Since cloning of the tumour suppressor gene for Neurofibromatosis type 1 in 1990, significant advances have been made in understanding the molecular pathways underpinning this disorder and how they relate to clinical features of the disease, including tumour related complications. A range of tumours are associated with NF1 including optic pathway glioma, juvenile pilocytic astrocytoma, brain stem glioma and plexiform neurofibroma which has the potential to transform to malignant peripheral nerve sheath tumour. Neurologic complications are many and varied depending on tumour type and location.

A number of candidate medications have been proposed in recent years, based on both the signalling pathways disrupted in NF1, and other specific characteristics of tumour biology. These agents will be reviewed with particular reference to plexiform neurofibromas and evidence of efficacy and tolerability available to date. Specific examples of children treated at The Children's Hospital at Westmead will be included.

The design of clinical trials for evaluation of medical therapies for plexiform neurofibroma present challenges related to the complexity and variability of these tumours. The development of appropriate

functional outcomes in addition to evaluation of radiographic tumour response has been recognised as an important area for inclusion in ongoing treatment trials.

15:00 **EMERGING THERAPIES IN TS** **H1B**
John Lawson

Dr John Lawson is a paediatric neurologist at The Sydney Children's Hospital campus of The Sydney Children's Hospitals Network. His interest and expertise includes the management of the neurologic complications of neurocutaneous disorders, specifically Tuberous Sclerosis Complex.

This practical review of the latest treatments available for Tuberous Sclerosis summarises the published trials, reflecting on local experience.

15:20 **NEUROLOGICAL MANIFESTATIONS OF HYPEREKPLEXIA** **H1B**
Grahame Wise

Dr Grahame Wise is Emeritus Professor at the University of New South Wales, School of Women's and Children. He trained in Paediatric Neurology 1967-1970 at the Albert B Chandler Medical School, University of Kentucky, Lexington, Kentucky, USA.

On return to Australia he formed the Department of Paediatric Neurology at the Prince of Wales Children's hospital later to become the Sydney Children's Hospital. He remained Head of that Department for the next 30 years. Under his guidance the department grew with particular expertise in general clinical neurology, epilepsy and neuromuscular disease.

Dr Wise was responsible for undergraduate and postgraduate teaching, wrote many articles for journals and had huge clinical responsibilities. Since official retirement he has continued to offer quarternary opinions on difficult cases across SCHN, he actively teaches and regularly presents at paediatric neurology meetings.

His contribution to Australian Paediatric Neurology is immense.

Two affected offspring of this non-consanguinous couple have been followed for thirty years.The compound heterozygous mutations responsible for this recessive form of hyperekplexia, affecting the SLC6A5 gene coding for the glycine transporter GlyT2 has been recently reported[1,2].

Startles were first noticed in utero from thirty weeks gestation. An uneventful delivery was followed by recurrent episodes of stiffening, at times with apnoea, and at times repetitive, provoked by facial, especially nasal stimuli and noise, unresponsive to phenobarbitone,phenytoin and pyridoxine, and suppressed by clonazepam. Face washing and bathing have continued to precipitate these events, and showering and swimming require close supervision.

Hypertonia, without pyramidal signs, progressively resolved over early years, but clumsiness remains.

Volitional conjugate gaze difficulties, resulting in head thrust and apparent gaze avoidance; and variable dysconjugate gaze and fine nystagmus were maximal in first year. Episodes of brief motor arrest, and of prolonged repetitive stiffening with retained consciousness have occurred, seizures were questioned, but electroencephalograms have been normal. Falls have not been prominent. Mild-moderate intellectual disability required special schooling, and they have limited independence, but continue to mature socially.

Conclusion: The stiff, apparently fitting newborn deserves a tap on the nose. Eye movement disorders and intellectual disability sometimes accompany hyperekplexia, and startles and hypertonia become much less intrusive with age.

References:

1. Rees et al, 2006, Nature Genet. 38, 801-806
2. Carta et al, J Biol Chem. 2012;287(34):28975-85.

SUNDAY 5TH MAY 2013

Time	Event	Speaker	Venue
	Morning Platform Session (Chair: Michael Cardamone)		
09:00	Platform presentations		H1B
10:45	**Morning tea**		H1A
	Late Morning Session (Chair: Hugo Sampaio)		
11:00	Clinical and pathophysiological insights in assorted neuropathies	Michelle Farrar	H1B
11:30	The exome approach to NMJ disorders	Gina O'Grady	H1B
12:00	An update into new treatments for DMD	Monique Ryan	H1B
12:30	Feedback from research collaboration special interest group	Russell Dale	H1B
12:45	**Lunch**		H1A
13:30-14:30	Trainee platform award		H1B
	Recognition of service award		H1B
	ANZCNS – a year in review		H1B
14:30	Conference close		H1B

09:00-10:45 **PLATFORM ABSTRACTS** **H1B**

09:00 **An open label clinical pilot study of resveratrol as a treatment for Friedreich ataxia**

Eppie Yiu, Royal Children's Hospital, Melbourne

Background: Friedreich ataxia (FRDA) is due to a triplet repeat expansion in the FXN gene, resulting in deficiency of the mitochondrial protein frataxin. Resveratrol is a plant-derived polyphenol. It was identified to increase frataxin expression in cellular and mouse models of FRDA, and has anti-oxidant properties.

Methods: This trial evaluated the effect of two different doses of resveratrol on lymphocyte frataxin levels over a 12-week period in individuals with FRDA. Secondary aims evaluated the effect on FXN mRNA, oxidative stress markers and clinical measures of disease severity. Safety and tolerability were studied.

Results: 24 participants completed the study; 12 received low-dose resveratrol (1g daily) and 12 high-dose resveratrol (5g daily). Lymphocyte frataxin levels did not change in either dosage group [low dose group change: 0.08 pg/µg protein (95% CI -0.05, 0.21, p=0.21); high dose group change: 0.03 pg/µg protein (95% CI -0.10, 0.15, p=0.62)]. Improvement in ataxia was evident in the high-dose group (change in International Cooperative Ataxia Rating Scale, ICARS -1.9 points, 95% CI -3.1, -0.8, p=0.004) but not the low-dose group (change in ICARS -0.3 points, 95% CI -3.2, 2.6, p=0.80). Significant improvements in hearing and speech were demonstrated in the high-dose group. A significant decrease in the oxidative stress marker plasma F2-isoprostanes occurred in the high-dose group. No serious adverse events were recorded. Gastrointestinal side effects were a common, dose-related adverse event.

Conclusions: This trial provides evidence for high-dose resveratrol as a potential disease-modifying therapy for FRDA. A placebo-controlled trial is required to assess its benefits further.

09:15 **Whole exome sequencing is effective in achieving a diagnosis in rare recessive childhood neuropathies**

Kavitha Kothur, Children's Hospital Westmead

Aim: To describe the utility of whole exome sequencing in the diagnosis of childhood inherited peripheral neuropathy.

Case Series: The inherited peripheral neuropathies are a genetically heterogeneous group of disorders with variable clinical onset and severity. Traditionally, inherited neuropathies are classified on basis of inheritance and nerve conduction findings, to target specific genes for sequencing. With the rare recessive neuropathies, this may involve significant cost and time before a diagnosis is achieved. The advent of novel sequencing technologies has led to the identification of numerous novel genes causing peripheral neuropathy but is not widely used for screening known genes. We describe two children with early-onset sensorimotor neuropathy, one with a sporadic demyelinating neuropathy, and the other presenting as part of a

dominant pedigree with demyelinating neuropathy, where extensive genetic testing had not revealed the causative gene. DNA from both families was analyzed using whole exome sequencing. This revealed homozygous mutations in SH3TC2in one family, causing CMT4C, in the first child who had a rapidly progressive sensorimotor neuropathy with proximal weakness, but without early onset scoliosis that is a universal feature of CMT4C. Exome sequencing in the second family revealed the unusual occurrence of compound heterozygous mutations in the FIG4, causing CMT4J, in both the mildly affected mother and the affected child.

Conclusion: Whole exome sequencing is not only a useful research tool for identifying novel genes causing childhood neuropathy, but can also be a useful diagnostic tool. Early diagnosis facilitates the understanding of prognosis, genetic counseling, and recruitment into natural history and treatment trials.

09:30 **Median neuropathy in paediatric mucopolysaccharidosis**
Trupti Jadhav, Royal Children's Hospital, Melbourne

Background: Compressive median neuropathy at the wrist (MN) is rare in children but is a recognised complication of mucopolysaccharodosis (MPS). Early detection and surgical correction is essential to limit functional loss and improve quality of life in children with median neuropathies caused by storage disorders.

Methods: Clinical and electrodiagnostic data of ten children with MPS referred to the neuromuscular clinic at the Royal Children's Hospital, Melbourne from 2001-2012 were reviewed retrospectively. All had symptoms suggestive of MN. All subjects underwent nerve conduction studies (NCS) including bilateral median and ulnar motor and sensory studies. The presence or absence of MN was determined and its severity graded according to neurophysiologic criteria.

Results: Three children had MPS type I, 4 type II, 1 type III and 2 type IV. All had progressive hand dysfunction, pain and/or wasting of thenar muscles. Seven patients had median neuropathies (six bilateral, one unilateral). Three had mild, 2 had moderate and 2 severe MN. Repeat studies in two subjects showed recurrence some years after decompressive surgery.

Conclusion: Compressive median neuropathy at the wrist is common in children with MPS. This study did not examine asymptomatic children but suggests that screening NCS should be considered at an early age in all children with these disorders, and that any symptoms of this condition should prompt neurophysiologic evaluation.

09:45 **Epileptic spasms in infants with Vitamin B12 deficiency**
Tejaswi Kandula, Sydney Children's Hospital

Background: Cobalamin or Vitamin B12 as a co-factor has a crucial role in DNA synthesis and cellular energy metabolism. Deficiency of cobalamin or its metabolites in infants can have significant deleterious impact on neurological development. This can present

with poor feeding, hypotonia, microcephaly, developmental delay and rarely, seizures. Infantile spasms as a manifestation of epileptic encephalopathy in the setting of cobalamin deficiency have only been reported in a handful of cases, usually associated with Methylmalonic aciduria.

Case Series: We describe three infants with epileptic spasms, encephalopathy and severe cobalamin deficiency at spasm onset. Age range at presentation was 4 to 9 months. Developmental delay at commencement of treatment ranged from mild to severe. Other biochemical and haematological markers of cobalamin deficiency were not seen consistently in all patients. Cobalamin supplementation was undertaken alongside management of seizures in accordance with currently accepted best practice.

Outcome: All patients were seizure free at follow up and demonstrated significant improvement in developmental status. This might represent a subset of patients with epileptic spasms with a good prognosis if treated promptly. The role of cobalamin in the pathogenesis of spasms requires further research and clarification.

10:00 **Recurrent coma**
Richard Webster, Children's Hospital Westmead

Recurrent coma in childhood is unusual and there is a large differential diagnosis. Previously, a platform presentation discussing recurrent episodic coma was presented at the ANZCNS Annual Scientific Meeting in Port Arthur in 2011. Differential diagnoses for recurrent episodic coma that were considered at that time were: hemiplegic migraine, non-convulsive status epilepticus, CADASIL, metabolic disorders, intoxication, auto-immune disorders and Klein- Levin syndrome. A further update on this topic is available and this will be discussed together with a framework for investigating recurrent paediatric coma.

10:15 **Paediatric narcolepsy - interesting case examples to keep you awake**
Deepa Srinivasan, Children's Hospital Westmead

Background: Narcolepsy is a disorder of sleep that is characterised by excessive daytime somnolence and the abnormal occurrence of some rapid eye movement sleep phenomenon into wakefulness[1]. Two symptom peaks are identified (the second decade and mid third decade of life), with much of the literature concentrated on the adult population. Narcolepsy in childhood compared to the adult population, appears to have a broad aetiological basis with the influence of genetic, environmental and autoimmune factors resulting in a diverse constellation of presenting symptoms[2].

Case Series: We present 5 cases of recently diagnosed narcolepsy in the paediatric population.

Conclusion: In this series the presenting history and pathogenesis show considerable variation, and we therefore highlight important

clinical, electroencephalographic and polysomnographic markers to help identify this condition in childhood.

References:
1. Hood BM, Harbord MG: Paediatric narcolepsy: complexities of diagnosis, Journal of Paediatric Child Health, 2002 Dec; 38(6):618-21.
2. Peterson PC, Husain AM: Pediatric narcolepsy, Brain Development, 2008 Nov; 30(10):609-23.

10:30 **Systematic review of the prehospital use of midazolam for prolonged seizures**

Mohammed Shabeed Chelakkadan, Sydney Children's Hospital

Background: An increasing number of children with epilepsy are being prescribed buccal or intranasal midazolam for home use in the management of prolonged seizures. Intranasal or buccal midazolam has been found be as effective as rectal diazepam in controlling prolonged seizures in hospital based studies[1,2,3]. In Australia, a guideline was developed in 1995 for the home use of rectal diazepam in children, however there are no such guidelines for the prehospital use of midazolam.

Objective: Review the literature and develop a guideline on out of hospital use of midazolam for the treatment of prolonged seizures.

Results: Randomised controlled trials have shown increased or comparable efficacy of buccal or intranasal midazolam when compared to rectal diazepam in controlling prolonged seizures in the hospital setting[1,2]. Limited community based case series report similar findings[2,3]. Social acceptance is significantly higher with buccal midazolam. The side effects, most significantly respiratory depression, were found be less or similar to rectal diazepam[2,3]. A high incidence of significant respiratory depression, up to 5%, was observed in better designed (prospective RCT) studies[1].

Conclusion – There are few community-based case series that examine the efficacy and side effects of buccal midazolam. There is no clear data available on the indications for prescribing and the profile of patients who may be at higher risk of having respiratory depression. A prospective RCT suggests a high rate of respiratory depression in hospital use. This is a major concern poorly addressed in case series. A proposed guideline has been developed.

Proposed guideline: Buccal/intranasal midazolam could be considered for home use when:

- > 6 months of age
- No major risks of respiratory depression
- Competent family who agree to undertake first aid training
- Informed consent undertaken by the referring specialist detailing the risks and benefits of the medication and that it is off-label use
- Plus one of the following:
  - A pattern of prolonged seizures (>10mins)
  - History of severe epilepsy and remote from emergency services

References:

1. John McIntyre, Sue Robertson, Elizebeth Norris, Richard Appleton, Willim P Whitehouse, Barabara Phillips, Tim Martland, Kathleen Berry, Jacqueline Collier, Stephanie Smith, Imti Choonara (2005) Lancet. 366, 205-210.
2. Rod C Scott, Frank M C Besag, Brian G R Neville (1993) Lancet. 353, 623-626
3. Bibek Talukdar, Biswaroop Chakrabarty (2009) Brain & Development. 31, 744-749

11:00 **CLINICAL AND PATHOPHYSIOLOGICAL INSIGHTS IN ASSORTED NEUROPATHIES** **H1B**

Michelle Farrar

Dr Michelle Farrar is a paediatric neurologist at Sydney Children's Hospital with a clinical interest in neuromuscular disorders. Her research includes investigating the mechanisms and the possible prevention of neurodegeneration in spinal muscular atrophy and other inherited neuropathies. She was awarded a PhD in 2012 for her thesis titled 'The pathophysiology of spinal muscular atrophy'.

Clinical and functional assessments combined axonal excitability studies have recently been applied to various paediatric peripheral neuropathies and provided important insights into axonal ion channel function, to shed light on pathophysiological mechanisms. This presentation will initially review the basics of action potential propagation, axonal ion channel functions and membrane properties that influence nerve excitability, the principles of clinical nerve excitability testing and the reported findings in various paediatric disorders. These studies are being developed to potentially monitor disease progression and the response to potential therapies.

11:30 **THE EXOME APPROACH TO NMJ DISORDERS** **H1B**

Gina O'Grady, Nigel Clarke & Manoj Menezes

Dr Gina O'Grady is a paediatric neurology trainee currently working as the Neurogenetics fellow at the Children's Hospital at Westmead.

Dr Nigel Clarke is a clinical geneticist and researcher who specialises in the diagnosis and pathogenesis of inherited muscle disorders.

Dr Manoj Menezes is a paediatric neurologist at the Children's Hospital at Westmead. His research interests include childhood inherited neuropathy and neuromuscular disease.

Congenital myasthenic syndromes (CMS) are a heterogeneous group of diseases and although uncommon, they are important to diagnose because of the potential for therapeutic intervention.

Mutations in 12 genes expressed at the neuromuscular junction can cause CMS. The clinical manifestations are variable ranging from early-onset fatigable weakness to limb-girdle muscle weakness, which may be misdiagnosed as a myopathy or dystrophy.

We present a series of patients with DOK7 mutations who had variable myasthenic symptoms and a girl with congenital myasthenia syndrome due to GFPT1 mutations that was initially thought have a congenital muscular dystrophy. We will discuss the challenges and the most useful clues to diagnosing CMS. We also report preliminary data that indicates neuromuscular junction dysfunction in some patients with centronuclear myopathy due to DNM2 mutations, and we report patients' responses to pyridostigmine treatment.

12:00 **AN UPDATE INTO NEW TREATMENTS FOR DMD** **H1B**

Monique Ryan

Associate Professor Monique Ryan is a paediatric neurologist in the Children's Neurosciences Centre, Royal Children's Hospital, Melbourne Australia, where she is head of the neuromuscular clinical research program and multidisciplinary Neuromuscular Clinic. Her research interests include natural history studies of paediatric neuropathies and clinical trials of new therapies for muscle diseases, neuropathies and myasthenic syndromes of childhood. She is a member of several international neuromuscular research consortia, a board member of CINRG and a member of the TREAT-NMD therapeutic advisory committee.

Duchenne muscular dystrophy is the most common progressive neuromuscular disorder of childhood and is invariably fatal, but with supportive therapies life-expectancy in DMD has increased into the third and fourth decade. There is as yet no curative treatment for DMD, but this condition is a focus of national and international laboratory-based and clinical research. Several Australian centres are involved in DMD-related research through the ANN, CINRG, TREAT-NMD and other networks. This presentation will provide an overview of current management and future therapies for DMD.

POSTER ABSTRACTS

GLUT-1 deficiency presenting with hemiplegic migraine

Sophie Calvert & Shekeeb Mohammad, Royal Children's Hospital, Brisbane

Objective: To describe a case of GLUT-1 deficiency manifesting with hemiplegic migraine and absence seizures with good response to the Modified Atkin's diet.

Background: Glucose transporter-1 deficiency syndrome (GLUT1-DS) is a treatable epileptic encephalopathy caused by mutations in the SLC2A1 gene resulting in impaired glucose transport into the brain. Patients with GLUT-1 deficiency typically present with seizures resistant to conventional antiepileptic drug treatment. Paroxysmal dyskinesia and movement disorders have recently been described as part of the phenotype. The only effective treatment is the ketogenic diet. Mutations in SLC2A1 have been reported in children with alternating hemiplegia of childhood. A case report has documented migraine headaches and GLUT1-DS in two related children, whose symptoms improved on the ketogenic diet[1]. Another case report documented paroxysmal episodic dyskinesia, absence epilepsy and hemiplegic migraines in a previously undiagnosed 25 years old woman[2].

Case report: we report the case of an 8 years old boy with a working diagnosis of ataxic cerebral palsy who had a 3 year history of weekly headaches with hemiplegia. These episodes lasted 20-30 mins at a time and were associated with photopsia, pallor, nausea, phonophobia and photophobia. His mother, maternal uncle, two maternal aunts and maternal grandmother had similar headaches, sometimes associated with hemiparesis. He also had a history of blank episodes consistent with absence seizures. He had upper motor neuron signs in the legs, ataxic gait, scanning speech and an intention tremor. Previous investigations included two normal brain MRIs, negative testing for mitochondrial point mutations and normal serum lactate. CSF tested with the second MRI at 8 years of age showed a glucose of 2.0 mmol/L with a paired plasma glucose of 5.6 mmol/L (CSF: plasma ratio 0.36). A provisional diagnosis of GLUT-1 transporter deficiency was later confirmed by a missense mutation in the SLC2A1 gene. He was started on the Modified Atkins Diet restricting his carbohydrate intake to 25g/day but liberal fat intake. After three months on the diet his headaches had resolved; his neurological signs - gait and tremor as well as his cognition had improved. His headaches recurred when there were lapses in his diet.

Conclusions: The spectrum of GLUT-1 DS is expanding. We draw attention to an uncommon presenting symptom of hemiplegic migraine which resolved on treatment but recurred with lapse in treatment.

References:

1. Aintzane Urbizu , Ester Cuenca-León, Miquel Raspall-Chaure, Margarida Gratacòs, Joan Conill et al. Paroxysmal exercise-induced dyskinesia, writer's cramp, migraine with aura and absence epilepsy in twin brothers with a novel SLC2A1 missense mutation. Journal of the Neurological Sciences 295 (2010) 110–113
2. Schneider SA, Paisan-Ruiz C, Garcia-Gorostiaga I, Quinn NP, Weber YG, Lerche H, et al. GLUT1 gene mutations cause sporadic paroxysmal exercise-induced dyskinesias. Mov Disord 2009;24:1684–8

Thymoma and juvenile paraneoplastic myasthenia gravis

Eunice Chan, Andrew Kornberg & Maryam Shamassi, Royal Children's Hospital, Melbourne

Juvenile myasthenia gravis is an uncommon acquired autoimmune disease with onset before 16 years of age. Thymoma, a rare malignancy in children, is even more rarely the underlying aetiology for juvenile myasthenia gravis. Few paediatric case reports have been described in detail over the past three decades. As in later-onset myasthenia gravis, juvenile myasthenia gravis can present prior to the identification of a thymoma and after the removal of a thymoma.

We report a case of a 13½ year old adolescent who presented with typical features of new onset juvenile myasthenia gravis, who was found to have a large multicystic thymoma on routine work up. We also reviewed the limited

literature on the association between juvenile myasthenia gravis and thymoma.

Conclusion: Juvenile myasthenia gravis can, on rare occasions, be the presenting paraneoplastic features of an underlying thymoma in children as in adults. Diagnostic work up should include chest imaging to exclude the presence of a thymoma.

Kaposiform haemangioendothelioma and Coats' disease complicating neurofibromatosis type 1: a case report

Simone Ardern-Holmes & Richard Webster, Children's Hospital Westmead, Sydney

Background: Neurofibromatosis type 1 (NF1) is a neurocutaneous disorder with a tendency to formation of tumours causing functional impairment both within and outside the nervous system, including vasoproliferative tumours. An association with kaposiform haemangioendothelioma (KHE) has not yet been reported. Significant visual loss can be associated with Coats' disease (retinal telangiectasia with retinal and subretinal exudates) which has rarely ocurred with NF1, in addition to optic pathway glioma.

Case report: A 2 year old boy with paternally inherited NF1 presented with café au lait spots, and a mass on the left arm resembling a plexiform neurofibroma, commonly associated with NF1. Progressive enlargement of the lump occurred with pain, affecting the function of the left arm. MRI showed an infiltrative lesion atypical for a plexiform neurofibroma. Surgical debulking demonstrated KHE on histopathology and was associated with functional improvement. The radiographic, clinical, and histologic features, and treatment options for KHE are reviewed and contrasted with plexiform neurofibroma. Neuroimaging demonstrated Coats' disease in addition to optic pathway glioma with associated bilateral visual impairment. Treatment with laser photocoagulation therapy and chemotherapy were provided to optimise visual function.

Conclusion: Loss of the tumour suppressor function of neurofibromin in NF1 is associated with neuroectodermal tumours and may rarely be associated with vascular tumours of mesodermal origin such as Coats' disease. We hypothesise a similar mechanism for the occurrence of KHE in this child. KHE should be considered in the differential diagnosis of presumed plexiform neurofibromas with atypical increased vascularity and infiltrative features.

A case of presumed isolated autoimmune autonomic neuropathy

Erik Andersen, Royal Children's Hospital, Melbourne

Background: Autoimmune autonomic neuropathy is an uncommon disorder with acute disruption to the parasympathetic and sympathetic autonomic nervous system. Patients present with varied symptoms including visual disturbance, vomiting, dizziness and urinary retention, and diagnosis may be difficult or delayed. Intravenous immunoglobulin (IVIG) is the mainstay of treatment with immunosuppressants as an adjunct in addition to symptomatic management.

Case report: A 12 year old girl presented with a 4 week history of dysphagia, vomiting and associated 9 kg weight loss with marked constipation following an upper respiratory tract infection two week's previously. She also reported visual disturbance over the same timeframe. On examination she was a well girl with a soft abdomen and stool palpable in her left lower quadrant. She had bilaterally dilated pupils with a sluggishly reactive right pupil and a non-reactive left pupil. Otherwise her neurological exam was normal. She was admitted under Gastroenterology with normal gastroscopy and a barium study showing gastroparesis. On further discussion a history of reduced lacrimation was obtained and a referral to the Neurology service was made. After examination and work up a diagnosis of dysautonomia was made and IVIG was given and oral prednisone commenced, with limited improvement at 7 weeks follow-up.

Conclusion: "Pure" dysautonomia is rarely seen, with autoimmune autonomic dysfunction generally being associated with a more diffuse neuropathy such as Guillain Barre syndrome.

This case demonstrates a rare condition which initially presented with what were thought to be unrelated symptoms. Current theories of pathogenesis and treatment options will be reviewed.

Outcome of early treatment in PNPO deficiency - a case series and literature review

Kate Riney, Mater Children's Hospital, Brisbane & Dave Coman, Royal Children's Hospital, Brisbane

Introduction: PNPO deficiency results in an early onset neonatal encephalopathy that can be severe and fatal if not detected and treated early. The condition is rare and can mimic hypoxic ischemic encephalopathy. Fertility problems are reported in parents of offspring with PNPO deficiency and preterm labour is common. In this paper we report three cases of PNPO deficiency that are the only known cases in Australia.

Case series: Three infants diagnosed with PNPO deficiency in early life are reported. All three were treated early and have had normal developmental outcomes. Globally there are only 4 known cases of PNPO deficiency that are known who were treated in the first days of life and information regarding the outcomes of these cases has not yet been published.

Conclusion: There is a risk of infants with PNPO deficiency being mistakenly assumed to have severe hypoxic ischemic encephalopathy. Clinicians should be vigilant and consider this metabolic disorder in early onset epilepsy, particularly if there is associated encephalopathy. The developmental outcomes reported for these three cases are informative as there is currently no literature reporting such positive outcomes when cases are diagnosed and treated early.

NOTES

NOTES

NOTES

Dr Damian Clark, Dr Suzanna Thompson, Dr Clair Pridmore and Dr Nick Smith would like to invite you to attend the 3rd ANZCNS Annual Scientific Meeting in Adelaide in May 2014.

anzocns

THE AUSTRALIA AND NEW ZEALAND CHILD NEUROLOGY SOCIETY