

Report back from the International Child Neurology Congress, Grand Hyatt, Mumbai

15-18th November 2018

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Protecting the Developing Brain was the title of this year's ICNA conference held in Mumbai, India. The conference was opened by the outgoing president, Prof Ingrid Tein. There was a minute of silence to honour the memory of Prof Linda de Meirleir, who made a huge contribution to knowledge of child neurology and to the ICNA. Professor Jo Wilmshurst from Red Cross War Memorial Children's Hospital was welcomed as the incoming president of ICNA, a proudly South African moment! This is a brief overview of the talks given.

Thursday 15th November Plenary 1

Non infective Acute Encephalopathy – Prof Jacob John initiated the plenary sessions with a talk about a disease affecting undernourished children from rural North India. After much detective work it was discovered to be related to ingestion of seeds of the Cassia plant, as suspected by local health workers. Hepatomyoencephalopathy had initially been thought to be a form of viral encephalitis.

Plenary 2: Funny eye and head wiggles and other confusing ocular motor disorders in kids – David Zee

David Zee showed videos of different types of nystagmus, (see saw/windmill/convergence/pendular). He discussed mechanisms holding eyes still: a) vestibular (peripheral or central); b) gaze holding (brainstem and cerebellum); c) mechanisms that keep eye movements calibrated (maladaptation and sensory deprivation (nystagmus of the blind)) and d) ion channels that control membrane stability (saccadic oscillations). Memantine can be used for congenital nystagmus.

Other interesting movements i) periodic alternating nystagmus – changes with direction of gaze due to a lesion in the cerebellar nodulus, treatment with Baclofen ii) figure of 8 head oscillations due to absence of cerebellar vermis. This was an excellent clinical learning session.

Parallel Session 1 – Infection encephalitis in Asia

1) Tropical Encephalitis – Pratibha Singhi spoke about vaccine development and the importance of simple prophylactic measures.

2) Neurological complications of neonatal rotavirus infection – Jung Sook Yeom Rotavirus can affect healthy term infants causing seizures from 4-6 days of life. In Korea there have been neonatal outbreaks and a distinctive pattern of white matter injury has been identified with symmetrical periventricular and deep white matter restricted diffusion. [Brain Dev.](#) 2019 Jan;41(1):19-28. doi: 10.1016/j.braindev.2018.07.001. Epub 2018 Jul 18 Neonatal seizures and white matter injury: Role of rotavirus infection and probiotics. [Yeom JS¹](#), [Park JS¹](#), et al

3) HHV6 encephalitis – Hiroya Nishida CNS diseases associated with HHV-6 include febrile seizures, mesial temporal lobe epilepsy, multiple sclerosis, encephalitis, progressive multifocal leukoencephalopathy, chronic fatigue syndrome, cognitive dysfunction and myelitis. HHV-6 can infect multiple organs in humans and is a major causative pathogen of encephalopathy in Japan; either as a primary infection or a reactivation. Half of the patients are left with neurologic sequelae. Treatment is ganciclovir and foscarnet.

Parallel Session 2 – Recognition of neurometabolic organellar disorders and advances in treatment

Update in the treatment of Mitochondrial disorders – Ingrid Tein Mitochondrial disorders affect all systems except skin and hair Key systemic features: retinitis pigmentosa, short stature, diabetes mellitus, hypertrophic cardiomyopathy, renal tubular acidosis, sideroblastic anaemia, hypoparathyroidism, intestinal pseudo-obstruction, failure to thrive. Key neurologic features: oculomotor palsy, stroke, seizures, ataxia, myoclonus, fatigue/exercise intolerance, myopathy, rhabdomyolysis, mental regression, headache, cortical blindness, optic neuropathy, sensorineural hearing loss, dystonia, myelopathy, peripheral neuropathy.

Epilepsy phenotypes in mitochondrial disorders – 35-60% have epilepsy; 70% refractory-poor prognosis; 60% multiple seizure phenotypes; 45% mortality, higher incidence with complex I deficiency. 82% of seizures are preceded by other features-FTT, Dev delay, ataxia, other system disorder.

MELAS: Mechanisms of pathophysiology of MELAS 1)microangiopathy 2)neuronal/glial injury/cytopathy 3) spreading phenomenon. A protocol for treating stroke like events was suggested.

Therapeutic approaches include removal of noxious metabolites, administration of artificial electron acceptors, administration of oxygen radical scavengers, exercise and physical therapy, genetic counselling, gene therapy and germline therapy. Pharmacologic approach to restore mitochondrial function include i) upstream mitochondrial boosters eg. Resveratrol, AICAR, diet supplementation with NMN ii) target based approach eg. Oestrogen receptor related ligands, PPAR ligands, SIRT1 activators, AMPK agonists iii) phenotype based approach eg. yeast immortalized cell lines. Need for studies of ketodiet and cofactors.

Update on therapy of lysosomal Disorders Bwee Tien Polo There is high phenotypic variability in disorders of peroxisomal biogenesis, with some presenting only with ataxia or neuropathy. Infantile Refsum Disease can present with sensory, developmental, mild hepatic and mild cognitive problems. D Bifunctional protein deficiency is the most common single enzyme defect mimicking ZWS and can present with early seizures and hypotonia. There is a slowly progressive juvenile phenotype with cerebral atrophy, ataxia, cognitive decline, deafness, hyperreflexia and demyelinating neuropathy. VLCFA may be normal in ZW spectrum disorders. Adrenoleukodystrophy-over the age of 60 years more than 90% of women have symptoms. Fibroblast studies remain important for accurate diagnosis in LSD.

Platform 1- CNS Infection

Congenital Zika Syndrome(CZS) and Infantile Spasms – Lucas Alves Zika is transmitted by infected Aedes mosquitoes. In 2015 an outbreak in Brazil became a public health emergency. During pregnancy it can cause severe abnormalities in the foetal brain. A high incidence of infantile spasms was observed in infants with CZS and it should be considered in the aetiology Severe developmental delay is associated.

Acute Enterovirus D68 associated AFM – Jay Shetty EV D68 is a small single stranded RNA virus with properties similar to rhinovirus droplet spread; the incubation period is 3-5 days. The incidence of EBV68 AFP is increasing and in 2014 there were 22287 cases worldwide. MRI, CSF study and neurophysiology is recommended. Respiratory specimen (NPA/BAL/other) for Enterovirus and then EV D68.

Platform 2

Neurometabolic Profile of macrocephaly in infancy and childhood -Lobna Mansour 90 children 6m-6years with macrocephaly excluding hydrocephalus were reviewed. Canavan's 20; Gangliosidoses 20; Glutaric aciduria 17; Zellweger Syndrome 7; Metachromatic leucodystrophy 4, Vanishing White Matter 3; Joubert S 3, Familial 2, rest uncertain.

B12 deficiency in infancy Suresh Kumar: B12 deficiency should be looked for in infants with delayed milestones and was found in a small study to be twice as common in infants of vegetarian mothers.

Spectrum of riboflavinopathies from Southern India. Ten patients presented with respiratory, LMN facial and bulbar weakness, upper limb weakness, tongue fasciculations, hypotonia and deafness. 5/8 mutations in SLC52A3. NCS were normal. EMG showed 4Hz fasciculations. High dose riboflavin was initiated with improvement in most cases.

Analysis of 154 cases of Mitochondrial disease in Chinese children Yuking Shi 150/290(51%) had Leigh Syndrome(LS); 36% of these had mtDNA mutations. 73(25%) had MELAS. MtDNA mutations: 90/290 (55%). MELAS, 46%; Leigh S, 34%; LHON 6%. Large single deletions:4 /290. Complex 1 deficiency: 24%.

Platform 3 – Movement disorders

Genetic Spectrum of paediatric movement disorders – Kritika Tiwari Isolated dystonia – primary dystonia i) TOR1A gene assoc with DYT1, AD, action specific, treatment anticholinergic ii) THAP1 (HET) DYT6, AD, late onset fluctuating, dysphonia, treatment anticholinergic

Combined dystonia – Dopa responsive i) TH, DYT5b, AR, developmental delay, hypotonia, dopa-responsive ii) GCH1, DYT5a, AD, dystonia with diurnal fluctuation, dopa responsive. Dopa plus syndrome SGCE, DYT11, AD, myoclonus, dystonia, treatment Clonazepam.

Paroxysmal dystonia – i) PNKD, DYT8, AD, dystonia and chorea, treatment Carbamazepine ii) ATP1A3, DYT12, AD rapid-onset hemi dystonia, treatment Carbamazepine and flunarizine.

Complex dystonia – heavy metal metabolism i) PANK2, regression and dystonia, treatment with anticholinergic, syndopa, baclofen ii) PLA2G6, regression, seizures and dystonia, treatment with anticholinergic, syndopa, baclofen, DBS. Lipid storage disorders i) GLB1, late onset GM1 gangliosidosis, progressive dystonia, treatment DBS and BMT ii) HEXA Tay Sachs, clumsiness, dystonia, speech regression, cognitive decline, trial of Pyrimethamine

Anti-NMDAR Encephalitis in Children – Malaysian Experience – Leechin Wong

Clinical findings in 20 children: behavioural/psychiatric 100%, encephalopathy 95%, movement disorder 90%, seizure 70%, autonomic instability 85%, optic neuritis 5%, demyelination 5%. Prodromal symptoms – fever 11, URTI 6, GIT 5, headache 4. 70% had seizures, 70% of these were convulsive, 35% non-convulsive, 20% status epilepticus. Used IFA test to look for NMDAR antibodies – 75% had positive results in serum, 88% in CSF and 56% in serum and CSF. Only 15% had delta brush on EEG, along with other abnormalities. 30% had normal MRI, 30% had changes in white matter and 40% in grey matter. Half (n=10) responded to 1st line treatment – IVIG and IVMP, non responders were given 2nd line treatment – CP/Rituximab. At 2 year follow up 60% made a complete/near complete recovery, 35% had residual behavioural and mild to moderate learning disability, 5% had severe disability.

Rett syndrome in Taiwan – Deborah A Sival

Typical(MECP2) vs atypical – preserved speech(MECP2), early seizure(CDKL5), congenital variant(FOXG1)

MECP2 spectrum common mutations R168X, R255X, T158M, R106W, R270X, R133C. MECP2 genotype-phenotype correlation – mild R133C, R306C, severe – R255X, R270X. FOXG1 – microcephaly, severe ID with absent speech, epilepsy, stereotypies and dyskinesia, abnormal brain MRI. CDKL5 – EOOE, seizures <5months, spasms, myoclonus and prolonged GTC, refractory to AED

Tea Symposium 2 – Concussion: A disaster of gigantic proportions, Where is the balance? A pediatric neurology perspective

1) Traumatic Brain Injury in Children “Concussion” – Alcy R Torres

Post-concussion symptoms: - a) physical (headache, dizziness/balance, nausea, visual); b) emotional (anxiety, low mood); c) cognitive (attention, processing speed, memory) and d) Sleep/energy (hypersomnia/hyposomnia/drowsiness). Acute pathophysiology is related to early symptoms and shows recovery over a set time course; many pathophysiological changes can now be detected by advanced neuroimaging.

2) Concussion and Mild TBI – Biju Hameed

Traumatic brain injury is a major cause of death and acquired handicap in children and young adults in the developed world. In India RTA are the leading cause (60%) of TBI's followed by falls (20-25%) and violence (10%). Parental education and reassurance should include: - warning signs of more serious injury; description of injury and expected course of symptoms and recovery; instructions on how to monitor post concussive symptoms; prevention of further injury; management of cognitive and physical activity/test; instructions regarding return to play/recreating and school and lastly clear clinician follow up instructions.

Tea symposium 3

Pediatric arterial stroke imaging: Manohar Shroff 9/26 children with acute ischaemic stroke had arterial wall enhancement. The long term effects of gadolinium are unknown and 10-30 minutes extra imaging time is needed to image the arterial wall. Imaging of the neck and posterior circulation is important. Basilar stroke has

good outcome in 80% managed conservatively. Genetic mutations COL4A1/2 are associated with small vessel disease and porencephaly. Dissection is possible with severe tic disorders, congenital hyperelastosis.

Catheter Cerebral angiography Prakash Muthuswami Complication rate is 5% in experienced centres. Benefit of thrombolytic therapy in children under 18 years has not been established. Children have better collaterals and higher incidence of arteriopathy.

Functional neuroimaging predicting vulnerability and outcome-Nomazulu Dlamini AJNR2018 60% children with stroke in a first world setting have arteriopathy. Stroke under one year has high morbidity and mortality.

Friday 16th November

Session 1: Mimics of cerebral palsy

Mediation & Pranayam We began our day with some breathing exercises (pranayamas) from the art of living.

1) Treatable metabolic mimics of Cerebral Palsy: case studies – Brahim T Melaiki Prevalence of CP: 1 in 400 live births vs inherited metabolic disorders: 1/500 in developed countries. Metabolic disorders must be correctly diagnosed as early as possible:-a) some are treatable; b) the family can be provided with more accurate information regarding the prognosis and c) genetic counselling may be offered. Cerebral creatine deficiency is an important cause of dystonic “CP.”

2) Cerebral Palsy Mimics: An Overview – Sheffali Alternative diagnoses in suspected : a) with spasticity: spinal dysraphism, HSP (decreased vibration sense), leukodystrophy, arginase deficiency, Sjogren Larsson syndrome, biotinidase/folate deficiency; b) dyskinetic: DOPA-responsive dystonia, mitochondrial disease, Lesch Nyhan, Wilson’s disease, glutaric aciduria, GLUT1A, sepiapterin reductase deficiency (with oculogyric crises), cerebral creatine deficiency, neurodegeneration with brain iron accumulation; c) with ataxia: Angelmans, Jouberts, Friedrich’s Ataxia, Ataxia Telangiectasia(“wobbly”), Cockayne syndrome, Pelizeus Merzbacher disease, non-ketotic hyperglycinaemia. Neuraxonal dystrophy presents with regression, hypotonia evolving to spasticity, optic atrophy with nystagmus, onset 6/12-3y. Gene mutation in phospholipase A2 PLA2G6.

Red flags: i) history – no risk factors for CP, regression of skills, fluctuation in motor function, pure neurologic signs, positive family history ii) examination – dysmorphic, optic atrophy/retinopathy, pes cavus, evolving sensory signs. Arginase deficiency can cause spastic paraparesis with urinary urgency and reduced vibration sense. Careful history, clinical examination and neuroimaging are essential. The genetic and metabolic mimics of CP are all individually rare so a focused approach is needed; based on clinical clues and targeted investigations. Spastic diplegia in a child who was not premature should be further investigated.

Ref: Orphanet J Rare Dis. 2014 Nov 30;9:197. doi: 10.1186/s13023-014-0197-2. **Treatable inborn errors of metabolism presenting as cerebral palsy mimics: systematic literature review.** Leach EL, Shevell M, Bowden K, Stockler-Ipsiroglu S, van Karnebeek CD.

3) Metabolic/Genetic movement disorders mimicking Cerebral palsy – Wang-Tso Lee Many metabolic/genetic movement disorders mimic cerebral palsy, including neurotransmitter diseases and other neurometabolic diseases. Genetic syndromes or single gene mutation may also mimic CP. Hereditary spastic paraplegia or other AR cerebellar ataxia may be diseases mistaken to be CP. Genetic syndromes mimicking CP:- Rett syndrome, CDKL5 encephalopathy, FOXP1 (hyperkinetic)- related choreoathetosis, Prader Willi syndrome, Angelman Syndrome, etc. Some conditions are treatable eg AR cerebellar ataxia CACNA1 may respond to flunarizine or acetazolamide-give one month trial. TUBB4A(beta tubulin) leukodystrophy-hypomyelination with atrophy of cerebellum and basal ganglia.

4) Fukuyama Tribute

The Congenital Muscular Dystrophies: Continuation of a legacy – Carsten Bonnemann Prof Yukio Fukuyama was born in 1928 and died in 2014. He made ground-breaking contributions to epileptology and neuromuscular disorders.

CMD presents with low muscle tone and weakness at birth and in early infancy. Muscle biopsy shows dystrophic muscle disease. Primary Laminin alpha2 deficiency (LAMA2)- causes severe hypotonia with some independent walking but not achieved in complete deficiency. Arthrogyrosis is possible with contractures later. Mild motor neuropathy. Some have cystic leukoencephalopathy with or without posterior fossa malformations. 30% incidence of seizures, but intellectually mostly normal. Weak diaphragm.

Late development of external ophthalmoplegia is a marker for merosin deficiency.

Restoration of the basement membrane has been achieved in mouse studies and demonstrates the need for mutation specific approaches.

Collagen 6 disorders are recognisable clinically: hypotonia, weakness, loose skin, digital hyperlaxity, contractures, soft palms and abnormal scars. They have slow progression and tend to develop respiratory compromise while still ambulant-weak intercostals.

Gene therapy: -allele specific silencing with selective oligonucleotide ameliorates the phenotype. Pseudo exon skipping. CRISPR/Cas9.

Muscle-eye-brain disease there may be cobblestone lissencephaly and polymicrogyria. Gene replacement therapy for alpha dystroglycanopathies where the therapeutic gene would be made to fit inside the virus (in DMD gene too big).

As early as 1903 CMD was described by Frederick Eustace Batten. The Fukuyama Legacy is ongoing – from master phenotyping to next generation genetics to precision therapeutics.

5) Sheila Wallace Award

Child Neurology in East Africa Experience from the Coal Face – Pauline Samia East Africa has a young fast growing population and economy. It faces the double burden of communicable and non-communicable disorders. Progress has been made in research on malaria, Neuro-HIV and Epilepsy. Significant gaps remain in the understanding of neuromuscular disorders, behavioural disorders, genetic and preventable causes of disease of CNS. Strides have been made in training healthcare workers and advocacy; gaps remain in supportive services such as speech and occupational therapy. A significant need remains in improving public awareness and understanding of child neurology – critical in enhancing referral and advocacy efforts in the region.

Poster session: F-001, Category (epilepsy), Title – EEG services for children in Africa: Pilot survey of capacity and needs – Veena Kander. F-034, Category (epilepsy), Title – Epileptic Spasms in Southern Africa – Sharika Raga

Parallel Session 5: Precision medicine for Epilepsy

1)Neurometabolic epilepsies: Joy Yapito Lee: This session emphasized the importance of excluding treatable metabolic epilepsies-Glut 1, vitamin responsive, creatine deficiency, CLCN2, etc. Case study examples were shown. Antiquitin deficiency (pyridoxine def) can appear to respond to antiepileptic drugs initially and patients can remain seizure free after withdrawal of pyridoxine. Late onset variants have been described. Brain malformations do not exclude B6 deficiency. Oral dose 15-30mg/kg/day up to 200mg. Adults 500mg. 75% have IQ below 70 despite pyridoxine and a lysine restricted diet is starting to be recommended in addition to reduce the accumulation of toxic metabolites. L arginine 400mg/kg/day is also being recommended.

Serine transporter defects (Dx WES) multiple congenital abnormalities spina bifida, cataracts, hypogonadism-Infantile spasms. Rx serine 500-700mg/kg/day.

2)Personalised omics for epilepsies: Global opportunities and challenges – Clara Van Karnebeeck The outline for this presentation was the clinician's role – challenges and opportunities; P4 medicine for IEMs and Omics in 2018 (staying up-to-date, connector in multidisciplinary team, partnering with patient and family, phenotype and function 1st and lastly its evidence based and efficient. Clinical phenome+ exposome+molecular phenome.

3. Genomics in Epilepsy: Matsumoto Clinical Genetics 2018 New era-RNA sequencing detects aberrant splicing undetected by exome sequencing.

4. Treatment of metabolic epilepsy: Gabriella Horvath 7% of epileptic encephalopathy are thought to be secondary to an inborn error of metabolism. Possible treatments: ketogenic diet-reduces cox negative fibres in mitochondrial disease. Important to check clinical trials websites.

5. FIRES Sandip Patil 60% ongoing epilepsy; median 11 days to ketogenic diet. High dose Phenob in 5 p-seizure free, callosotomy in one stopped secondary generalisation.

Parallel Session 7: Autoimmune inflammatory neuropathies in childhood

Epidemiology and pathophysiology of autoimmune neuropathies in childhood – Yoram Nevo CIDP - slow onset (>28 days) or recurrent episodes (in children more common subacute onset and relapses), proximal and distal symmetrical weakness, hypo/areflexia, albuminocytologic dissociation, rare additional CNS involvement and paraproteinemia not described in children. There are various anti-ganglioside antibodies in GBS subtypes and variants and 4 functional regions where there is localization of injury in axonal GBS including nodes of Ranvier, paranodes, juxtaparanodes and internodes. Targeting nodal antigens may explain fast recovery following PE and IVIG. Antibodies to nodal, paranodal and Schwann cell-axon interaction proteins may explain fast recovery following IVIG and PE. In theory fast recovery or worsening is not due to remyelination/demyelination but due to blockade of humeral factors associated with saltatory movement at the node of Ranvier. This results in local conduction block rather than demyelination. In CD59 mutations clinical characteristics include children with early (infantile) onset relapsing neuropathy, relapses follow viral infections, additional clinical characteristics haemolysis during febrile illness and crisis. Findings that cast a doubt on diagnosis of GBS include persistent marked asymmetry, sharp sensory levels, persistent bowel/bladder dysfunction and fever at onset, >50 mononuclear WBC on CSF, presence of polymorphs in WBC in CSF.

Electrodiagnostics and differential diagnosis of autoimmune neuropathies in childhood – Malcom Rabie

NCS features in AIDP – early multifocal demyelination, SNAP absent/low, normal sural SNAP with reduced/absent median/ulna, needle EMG is non-specific with reduced recruitment initially, fibrillation potentials 3-4 weeks after onset. Earliest findings i) prolonged f-wave/poor repeatability (nerve root demyelination) ii) followed by prolonged distal latencies (distal demyelination) iii) conduction block or increased CMAP temporal dispersion (irregular) iv) NCV slowing (2-3 weeks after onset)

AMAN- CMAP amplitudes reduced early (2-3 days), normal sensory (SNAP), absent CMAP, needle EMG is helpful, denervation (psw) may occur early in AMAN (=axon loss), may have transient partial conduction block (distal, intermediate nerve) disappearing 2-5 weeks (reversible conduction failure)

AMSAN – SNAP reduced/often absent, CMAP reduced/absent, H-reflex absence may be only abnormality in 75% of MFS and BBE

Platform 5: Epilepsy

1) Ketogenic Diet: Do we Need 4:1 Ratio for Ketosis? – Purna Karnavat Lower ratios are equally efficacious when compared to higher ratios. They have benefits in terms of higher retention status, greater quantities and palatability. They have no associated disadvantages with relatively less side effects. Benefits like increased alertness, better behaviour were noted with higher frequency.

Cannabinoids: purified CBD effective for drop attacks starting at 10mg/kg/day with 2 weekly LFTs. Increase norelthazam levels and stiripentol but no difference in status epilepticus or SUDEP.

Tea Symposium 5: Update on Paediatric MS and demyelinating disease (on behalf of IPMSSG)

Recent advances in Paediatric Demyelination – Evangeline Wassmer Latest diagnostic criteria have been published by Thompson in Lancet Neurology 2018 along with revisions of the McDonald criteria. Prospective clinical trials in POMS include i) LEMKIDS – alemtuzumab ii) FOCUS – dimethyl fumarate iii) CONNECT – dimethyl fumarate iv) TERIKIDS – teriflunomide, v) PARADIGMS – fingolimod and vi) Natalizumab PK + PD.

Article entitled "Autologous haematopoietic stem cell transplantation for paediatric multiple sclerosis: a registry-based study of the Autoimmune Diseases Working Party (ADWP) and Paediatric Diseases Working Party (PDWP) of the European Society for Blood and Marrow Transplantation (EBMT).

Masterclass: M van der Knapp, N Wolff

Need for redefinition of leukodystrophies-any white matter component affected by a defect in a structural component or molecular structure.

H ABC- TUBB4A defect in beta tubulin causes hypomyelination of white matter with atrophy of basal ganglia and cerebellum. Axonal transport is defective.

Vanishing white matter disease: Eukaryotic Translation Inhibition Factor e IF2B1-3-mutation affects initiation of all mRNAs and regulates the integrated stress response. Mutations shut down protein synthesis and activate the cell death response. Preclinical studies of ISR inhibitor to activate eIF2B are promising.

Hypomyelination with brainstem and spinal cord involvement (HBSL) due to mutations in DARS may be partially steroid responsive.

CLIPPERS Chronic lymphocytic Infiltrative pontine perivascular enhancement responsive to steroids.

Saturday 17th November

1) Introduction to sleep - Lakshmi Nagarajan

Normal sleep: Newborns: 16-20 hours; 3-5 year olds:11-13 hours; 5-12 years olds:10-11 hours;12-18 year olds: 8-10 hours.

Sleep neurology in children: - Seizures and sleep, medication and sleep, apnoeas in sleep, parasomnias, Seizure mimics, SUDEP and sleep, excessive daytime sleepiness, narcolepsy, insomnia and dysomnia.

Sleep neurophysiology – the EEG is still the gold standard for defining sleep stages. Exciting times with rapid advances for sleep neurophysiology and neurology.

2) Challenges in evaluation and management of sleep disorder: Seizures & Seizure mimics in neonates & hypersomnolence – Lakshmi Nagarajan Seizures in neonates are a challenge to diagnose and treat. They are common and estimates of incidence variable. They include electroclinical, electrographic and clinical. The role of the EEG is important. There is debate regarding treatment (what to treat, with what to treat and how long to treat for). Neonatal seizures are associated with adverse neurodevelopmental outcomes.

EEG- Some non-epileptic events may mimic neonatal seizures (benign paroxysmal phenomenon, brain stem release phenomenon, subcortical seizures). Clinical seizures with EEG correlate can be subtle. 20-90% of EEG seizures can occur without clinical correlation. Seizure discharges may be variable in field, morphology, amplitude and clinical correlate.

Sleep & seizures – development & interpretation of sleep in the neonates is complex. Active sleep is the first sleep pattern to emerge during ontogenesis and neonates enter active sleep first. EEG background in wake and sleep good prognosticator for outcome in babies with seizures.

Hypersomnia disorders of central origin + epilepsy – excessive day time sleepiness is the most common presenting feature. History is very important. May be due to several causes: structural, HIE, Immune mediated, neurogenetic disorders and metabolic. Narcolepsy – type 2 more common but type 1 also rarely.

3) Challenges in evaluation and management of sleep disorder: Slow wave arousals Vs nocturnal epilepsy & narcolepsy – Shelly Weiss

It is often difficult to distinguish arousal parasomnias and nocturnal seizures on history. Video is very helpful. A routine EEG can miss events. Video EEG and/or Polysomnography are helpful in differentiating NREM parasomnia from seizure.

Segawa tribute Jean Pierre Lin Motion Movement action function-how dopamine dependent neural reward circuitry shapes the developing brain. The dopaminergic system is responsible for adaptation to the environment and is established early-limb and trunk movements precede breathing in utero. Periventricular leukomalacia affects thalamic radiation more than corticospinal tracts leading to sensory deficits. The role of sensory changes has been underestimated in CP.

Frank Ford Award

Fit for the Future: New insights into the childhood epilepsies – Helen Cross

Prof Cross gave an overview on the childhood epilepsies from 0-1 year of life: - 0-1 month [neonatal epileptic encephalopathies- benign familial neonatal seizures, EIEE (Ohtahara syndrome), EME (early myoclonic encephalopathy)]; 4-6 months [infantile epileptic encephalopathies – (Dravet Syndrome, West Syndrome, epilepsy in infancy with migrating focal seizures, lesional focal epilepsies)]; 1 year. For pre-surgical evaluation: - video EEG monitoring, MRI with specific protocol, functional imaging and age appropriate neuropsychology assessment.

Parallel session 9: Update on treatable immune-mediated CNS disorders: Diagnoses you don't want to miss

1) Paediatric Multiple Sclerosis – What is new? – Daniela Pohl

a) Epidemiology and risk factors – Paediatric onset MS is defined as onset of symptoms < 18 yrs. Approx. 5% of total MS population experience POMS.

b) Diagnosis – clinically or via MRI, lesions in at least 2 of 4 MRI areas (1. Periventricular; 2. Cortical/juxtacortical; 3. Infratentorial; 4. Spinal cord)

c) Disease characteristics and course – patients have a substantial risk at a young age for: - 1) cognitive deficits; 2) disability and 3) chronic progressive disease

d) Treatment incl. Controversies – new oral treatment option – Fingolimod – reduces relapse rate by 82%, significantly reduces brain atrophy, risk reduction of 77% in disability progression and lastly seizures/epilepsy reduced in 6%.

2) MOG-Encephalomyelitis – Updates on a New Syndrome – Silvia Tenenbaum

MOG is a member of the immunoglobulin superfamily. The presence of serum anti-MOG ab identifies a subgroup of children with an acquired CNS demyelinating condition, distinct from MS. It is important to test for MOG-IgG in all patients with suspected inflammatory brain, brainstem, optic nerve, and/or spinal cord involvement, as it can help to define the appropriate long-term management. A cell-based assay for full length human MOG as target antigen is the appropriate test. The overall prognosis is good. A subset of patients might be left with severe visual, motor, or bladder control dysfunction.

3) Anti-NMDAR encephalitis – update – Shekeeb Mohammad

Antibodies in children: - a) anti-NMDAR (most common autoimmune encephalitis with extreme spindles noted on EEG); b) anti-LGI1 (very rare); c) other autoantibodies (rare causes of AE (GAD, GABA-A-R); d) anti-AQP4 (rare cause of demyelination) and lastly e) anti-MOG (common association with demyelination).

The use of immune therapy rather than no therapy is more commonly associated with a better outcome and a lower rate of relapse. Early commencement is the gold standard.

4) Opsoclonus Myoclonus Ataxia Syndrome

This is an autoimmune neurological disorder targeting the cerebellum characterized by at least 3 of the following 4 features: - a) opsoclonus; b) myoclonos/ataxia; c) behavioural change and/or sleep disturbance (irritability, rage attacks) and d) neuroblastoma. The median age of onset is 18-22 months. Also occurs in older children and adults. Recent data suggests more common in girls (55-60%), affects all racial and ethnic groups and occurs worldwide. Need MRI neck to pelvis.

The take home points :- a) consider OMAS in differential diagnosis of all children with ataxia; b) neural crest cell tumour present in 50% of patients with OMAS; CT or MRI required for diagnosis in 20% of these and c) earlier, multi-agent immunosuppression may improve outcomes in OMAS. Must be able to differentiate between OMAS and ACA (acute cerebellar ataxia)

Tea Symposium 10: Drug refractory epilepsy and epilepsy surgery: A paediatric perspective

1) Introduction Drug Refractory epilepsy. A treatment perspective – Jorge Vidaurre

The impact of refractory epilepsy can have the following risks: - a) status epilepticus; b) SUDEP; c) limitations: driving, work, family, life and lastly d) depression and low self-esteem. Having resective epilepsy surgery can: - a) be highly effective in carefully selected cases; b) cost effective; c) improve psychosocial outcomes and d) considered after failing 2 AEDs. **BUT** less than 1% of patients are referred to epilepsy centres.

2) Pre-surgical evaluation (phase 1) for children with drug refractory epilepsy – Satya Gedela

a) Drug resistant epilepsy – 30% of epilepsy patients have DRE. Despite more than 14 new AEDs entering the market in the last 15 years, the rate of DRE has not been significantly reduced.

b) Pre surgical evaluation – in the USA only 1% of the 1 million patients with DRE are being referred to epilepsy centres for pre surgical evaluation. The delay from onset of DRE to surgery averages > 20 yrs, resulting in impaired social and educational development.

c) Safety in the epilepsy monitoring unit (EMU) – These included status epilepticus, seizure related falls, psychiatric adverse events (postictal psychoses) and lastly aspiration was rare with patients having seizures whilst eating and drinking during their LTM.

3) Paediatric Epilepsy. Importance of neuroimaging in the pre-surgical evaluation of children with drug refractory epilepsy – Harry Chugani High quality MRI studies are very important. When MRI is negative, PET scanning can still identify epileptic foci. Use of PET can help define the full extent of an MRI lesion and evaluate the integrity of surrounding brain tissue.

4) Epilepsy surgery in children. What is the aim? A realistic perspective – Helen Cross The primary outcome aims of epilepsy surgery is seizure freedom/reduction and secondary is neurodevelopmental gains and behavioural improvement. Epilepsy surgery in children is different, the evidence suggests that there is more to be gained by possibility of ‘cure’ in childhood, requires careful specialist evaluation and spectrum of pathology, justification for early referral where much to be gained and nothing to be lost.

5) Alternative therapeutic options for children with drug refractory epilepsy who are not surgical candidates – Jo Wilmshurst

a) Vagus nerve stimulation therapy is an adjunctive treatment for medically resistant focal epilepsy. It is expensive, there is a battery life span, there has to be training on how to use the device but side effects are usually minor.

b) The ketogenic diet shows promise for treating epilepsy syndromes (Angelmans syndrome, Dravet Syndrome, febrile infection-related epilepsy syndrome (FIRES), infantile spasms, Ohtahara syndrome, Tuberous Sclerosis complex etc.

c) Key points for a new KD team with limited resources – a physician, preferably a neurologist, and a dietician are mandatory. Adequate support must be in place for such families. Caregivers should be informed and given the opportunity to undertake the diet with the best compliance outcomes. There is clearly a role for the ketogenic diet as a treatment option for children with epilepsy. There is good supporting evidence that the diet can be safe and effective in a number of challenging epilepsies.

DBS and Dystonia JP LIN Dystonia at Evalina Children’s Hospital: 65% CP with 20% normal MRI; 19% idiopathic; 16% known genetic. In future there will be much smaller stimulators which will be able to record as well as stimulate. A major defect in dystonia may be sensory processing. SSEPs were abnormal in half of acquired cases.

Sunday 18th November

Plenary 3

Neonatal Seizures Lakshmi Nagarajan Orolingual seizures are the most common at onset-30% with right side affected in 78%. Ictal fast wave activity may be a marker for epileptogenic tissue. Levetiracetam is the most promising agent for treating NN seizures.

John Stobo Prichard Award: - Childhood Movement Disorders: Gene Discovery, Understanding Disease Mechanisms and Precision Medicine Approaches – Manju Kurian

The landscape is changing for childhood neurological disorders; exciting times to be a child neurologist; diagnosis is increasingly likely; understanding disease mechanisms increasingly possible; novel treatment are here or on the horizon (neuromodulation, gene therapy, anti-sense oligonucleotides, chaperones, novel agonists/molecules)

Parallel session: Integrating Paediatric Sleep Medicine into Child Neurology

1) Evaluation of nocturnal events: seizures, parasomnias and more - Sanjeev V Kothare

2) Hypersomnia disorders- narcolepsy and beyond – Suresh Kotagal This talk highlighted the 4 most common causes of arousals from sleep: - OSAS, parasomnias, nocturnal seizures (benign childhood epilepsy with centrotemporal spikes) and bruxism. For evaluation: 1) parasomnias to check for serum ferritin levels, 2) Polysomnography(PSG) for obstructive sleep apnoea, bruxism and restless leg movements and 3) video EEG for nocturnal seizures. The minimum age for an MSLT is 5 years, below that is not valid. Patients with narcolepsy can have dual conditions. Childhood hypersomnia disorders are diverse in aetiology, clinical features and PSG findings; history is key for early identification.

3) Sleep Disturbances and Children with neurodevelopmental Disabilities – Kiran Maski

- 1) unique sleep physiology (decreased REM sleep and increased slow wave sleep)
- 2) environment for sleep routine (establish a bedtime routine – bedtime checklist, bedtime pass)
- 3) Neurodevelopmental physiology (obesity, craniofacial structures)
- 4) Co-morbidities with NDD (i.e. anxiety/sensory problems)
- 5) medication side effects (rebound hyperactivity, weaning off medication)

4) Sleep disorders in special syndromes – Joanna E Wrede

Some specific syndromes that are risk factors of sleep disorders:-

- Prader- Willi syndrome (genetics chromosome 15q11.2-13, sleep disordered breathing (OSA, CSA, hypoxemia, hypoventilation), excessive daytime sleepiness (hypersomnia and narcolepsy)
- Trisomy 21 (genetic chromosome 21q22.3), sleep disorders (OSA, sleep onset and maintenance insomnia, excessive daytime sleepiness)
- Achondroplasia (caused by mutations in FGFR3 gene), sleep disorders (central sleep apnea)
- Chiari 1 malformation – sleep disorders (CSA and OSA)
- Neuromuscular disorders – sleep disorders (OSA especially in REM, sleep hypoventilation and CSA)
- Headache disorders – sleep disorders (OSA, insomnia)

The conference offered an opportunity to engage with many complex current issues and gave exciting insights into the future of paediatric neurology. The challenges are multiple and include the need to increase genetic screening in an equitable way so that precision medicine can be applied.

