ICNC 2016 Amsterdam May 1-5

This was a well-organised meeting in a good location. Whilst it was somewhat costly this was balanced by most of the group from SA sharing accommodation. There were over 1500 delegates and the topics ranged across state of the art updates to appropriate issues for LMIC. Overall it was a very useful meeting to attend both for the content and the networking with colleagues.

Of the SA group – many of the attendees contributed to the scientific activities as summarised below.

Presentations *

Plenary n=1; platforms n=4, posters n=9

Cape Town: Jo Wilmshurst*, Kirsty Donald*, Alvin Ndondo*, Ronald van Toorn, Regan Solomons, Tando Quvile*, Marie Wessels, Veena Kander*, Charles Hammond (Ghana)*, Louisa Mudawarima (Zimbabwe)*

Ex CT Edward Kija (Tanzania)*, Pauline Samia (Kenya)

Durban: Yavini Reddy*, Arushi Keshave*

Johanesburg: Gail Scher, Tiziana Aduc, Dorcus Wilson, Natalie Govender, Mike Lippert, Amina Bham, Marc Hauptfleisch*, Deborah Pearce, Firdose Nakwa*, Kaajal Parbhoo

Bloemfontein: Andre Venter

TOTAL N=25

Highlights of the last 2 years (Helen Cross)

About 20-30% of hospitalized patients have neurological issues. The longterm morbidity is high. Most management is symptomatic but more and more treatments are coming. There has been an explosion in understanding thanks to big cohort studies with good phenotyping of diseases. Added to this understanding in basic sciences have also expanded.

Understandings in **genetics and biomarkers** are leading to focused treatments which are impacting on the natural history of disease forming the bridge between basic science and clinical practice.

Childhood arterial ischaemic stroke (Lancet Neurol 2014 Mallick *et al*) The is a large study from the UK with 24 month outcome. It confirmed that stroke was more common in the younger population, and that those of black and asian ancestries were more affected. Acute systemic stroke was the most common in the form of arteriopathy. Children under one year of age with stroke are more likely to present with seizure, older children tend to present with motor signs. This data led on to collaborative studies in the form of the VIPS Stroke 2016, this

is a large multicenter study which recruited some 355 cases and looked at recurrence markers. The study found strong links with the increased risk with herpes infection.
Rivkin *et al* Stroke 2015 – TIPS couldn't complete – looked at antithromobsis in children – but couldn't recruit enough patients for the study and stopped early. So there is an ongoing project with standardized protocol which should hopefully eventually generate some useful data.
Autoimmune disorders (Lancet Neurol 2016 Graus *et al.)* This is first consensus definition of autoimmune encephalitis. From clinical presentation and biomarkers. It is a really good and useful report. For adults and children. This document is important to ensure that for ongoing studies there is consistency which will permit cross study comparisons.
Demyelinating diseases – the McDonald 2010 MRI criteria can be used in children, this guideline clarifies that even from a single MRI it is possible to diagnose MS – the age of lesions helps with this. This makes it possible to apply the diagnostic criteria and make the diagnosis earlier, leading to better counseling and treatment. It opens possible therapy which is used in adults. Further biomarkers have been identified AQP4+ neuromyelitis optica, there is evidence that there is a spectrum of disease seen, some patients have negative markers. According to the guidelines if the anitbodies are +ve only this one marker is needed to make the diagnosis, but now if it is negative or cannot be tested there are inclusion markers / signs that can be used to diagnose neuromyeltis opticala as an example.
MOG (myelin oligodendrocyte abs) have become increasingly important in all paediatric demyelinating diseases, especially ADEM cases (more so than in adults). If these Abs are found then this group are less likely to go on to have MS (helps with prognosis).
Epilepsy: New organization Berg *et al* 2010. Standardising the approach and terms used has been much needed and important to get consistency across studies. More recent versions have been submitted and the process is constantly under assessment. The organization has moved to start with the seizure type and the aetiology and to include co-morbidities. There are now 6 categories (genetic, structural, metabolic, immune, infectious, unknown). Unknown is a really important group as most of the new discoveries are coming out this this group. It is possible to belong to more than one group / aetiology – e.g. TSC – genetic and structural, metabolic e.g. GLUT1 – genetic and met, FIRES – immune and structural. Fisher *et al* – redefined the definition of epilepsy. Two unprovoked seizures, one unprovoked and chance of recurrence, syndromes etc. Spectrum of GLUT1 is a good illustration of the overlap and phenotypic review needed to understand the heterogeneity of disease phenotype. GLUT1 can have a predominant movement disorder, seizures and other co-morbidities. FOXG1 syndrome is a condition of developmental encephalopathy (Cellini *et al* DMCN) and the phenotypic picture is still evolving.
Genetic causes of epilepsy exploded recently. Trump *et al* J Med Genet 2016 highlighted the use of gene panels and showed that really targeted panels can lead to diagnosis in unexpected phenotypes. They took n=400pt with epilepsy and no diagnosis. In 46 patients the gene panel found a diagnosis and in 18% it was SCN2A as the biggest proportion confirmed. (The known phenotypes e.g. SCN1A had already been identified and were not included in the study ie. They

were only screening the truly "unknown" group). Onset of epilepsy under 2 months of age was the category with the highest pick up for many of the group. This system seems to illustrate a really good method for early diagnosis and approach to care.
KCNT1 – EIMFS – function mutation – role for quinidine in some
KCNQ2 – benign familial neonatal sz – but more severe encephalopathy groups occur– retigabine (potassium channel blocker) is a possible targeted treatment (sensitivity to sodium channel) (There is some worry as blue mucosa can occur but this appears to be less of an issue in the paediatric group). Other sodium channel blockers e.g. CBZ might work. This is important as one wouldn't normally consider using in this AED for this group of patients i.e. EE. Better seizure control is associated with developmental improvement.
mTOR inhibitors e.g. rapamycin are gaining increasing evidence to support their role in the management of epilepsy in patients with TSC. Extending on from this mutations in the *DEPDC5* region may also be of benefit from mTOR inhibitors. Further extending the potentially remedial phenotype.
Canabidiols (CBD). Devinsky *et al* 2016 – Lancet Neuro. Pure canabidiol seems to correlate with the best outcomes with good well prepared formuaitons e.g. GW Pharma. An open label multicentre study mostly completed. N=214 found minor AEs. Dravet and LGS were the group with relatively high responder rate. With the addition of clobazam the best outcomes occurred. Dravet syndrome showed some benefit over placebo but this data is still being analysed. LGS data is pending. As evidence is analysed this should influence licencing based on more definitive and better evidence. For the other case series and reports to date there has been a problem with the quality of the agent CBD, that the product extraction is variable and unreliable across studies. This has lead to conflicting statements about efficacy. Hence the latest study where this is controlled for should provide more accurate information.
Fenfluramine (Ceulemans *et al* 2012 Epilepsia), this is an old drug and there has been worry about cardiac AE, but these potential SE do not appear to be an issue in children. There is ongoing review for the role in children with Dravet. (Zhang *et al* Plos One 2016)
Spinal muscular dystrophy. Looking at upregulation of SMN – there appears to be possible therapeutic effect. Antisense oligonucleotides – with specific SMN function are delivered by intrathecal administration broadly to reach the spinal cord and lead to a wide area of effect. Chirboga *et al* and Azanetta C *et al* 2014 – are part of Phase III trials randomized placebo controlled trials which are underway and so far results look good with the suggestion that the disease can be converted to a less severe variant (i.e. type 1 to type 2). As such targeted therapy is underway.
Cong Zika syndrome – microcephaly, exaggerated primitive reflexes, arthrogryposis, epilepsy, dysphagia, intracranial calcification is a major issue an will continue to have worldwide implications in the future.

Neuroprotection for the developing brain: Michael Johnson
The excitatory glutamate synapse and NMDA receptors are critical for initiating the hypoxic-ischaemic cascade of injury. HIE impairs glutamate pumping out the synapse leading to extrasynaptic loss. CSF glutamate levels correlate with severity of neonatal encephaholpathy – as it accumulates in CSF (Raili Riikonen

studies and Lancet Neuro 2011, 10, 372-383). Accumulation of calcium entry and damage to mitochondria lead to eventual and progressive brain injury. If one gives MK801 (channel blocker for Calcium) before the insult this works well having a protective effect. Ketamine can also be brain protective. Magnesium is also a blocker and protector. There is a need to blocker NMDA related injury. Investigators looked at whether they could reduce evolution to Cerebral Palsy. They studies mothers who were at risk of having babies with brain insults (Karin Nelson Pediatric 1995 did the seminal work on this). Glutamate can have both trophic and toxic effects, when released within the synapse there are more trophic affects but when glutamate floods outside the synapse there are toxic effects. Excitatory NMDA receptors and nNOS are toxic to mitochondria and causes **delayed cell death**. Major pathway to cause brain damage (Lancet Neurology 2014 Hagberg *et al* "Mitochndria: The hub for injuries). Caspase activation is a common pathway to neuronal death from mitochondrial failure. This is why there is a delayed effect. Mitochondria and nucleus have delayed impact from damage (basically they don't know initially that they are dead!). Lorek *et al* – Ped Research 1994 – did important pig studies and illustrated the secondary energy failure, they found the role for the mitochondria which took hours to days to manifest demise after the insult. Rats which suffered ischaemia showed gradual activation of caspase. Little occurs for first 12 hours, then delayed energy failure and the appearance of apoptosis and necrosis. Therefore **cooling must occur early** – otherwise it is too late to reverse the damage. Imaging with near total asphyxia, there is delayed appearance in putamen and thalamus and perirolandic cortex which becomes evident a month after the insult. Despite a global insult only certain areas of the brain illustrate subsequent insult. Damages structures are connected by excitatory pathways ie. glutamate related. So the globus pallidus tends not to be affected and this is seen it is important to consider a mitochondrial disorder. So with an insult 98% of brain normal and the outcome of the child is often dyskinetic CP with the IQ often preserved. Outcome due to the selective vulnerability of glutamate where these selective circuits are affected in **a term infant**.

Insults can be divided into

- Near total asphyxia – eg 30 mins insult
- Partial prolonged asphyxia
- Watershed insult

The severity depends on brain temperature and the severity of NMDA mediated brain injury. In the 1990s the brain cooling concept was developed. Now it is routinely used for HIE events. Need to get in early – **before 1.5 hours of the insult**. Recommend cooling within 6 hours to be optimally effective. Cool for at least 72 hours and slowly rewarm. There is good evidence to support this (Gluckman *et al* Lancet, Shankaran *et al* NEJM 2005, Azzopardi *et al* NEJM 2009). Later studies found reduced rates of CP and better scores on Bailey's. Now the practice is widely adopted internationally. The cooling paradox illustrated that is is possible to develop a "simplified infant cooling device" (SCID) – this was designed by undergraduates (Jauhari *et al* DMCN 2011) based on concern as there are high rates of CP in India (Kim *et al* 2013) Evidence and Research has supported that a simple system could work in pigs and it should be possible to adapt equipment to simpler cheaper methods. The problem is that many babies have other types of injury e.g. **inflammation** which may be induced by hypoxic

injury (HI) (Strunk *et al* 2014). Microglia are activated by infection and excitotoxicty (Kaindl *et al* 2012). Dendrimers ("Tree-like polymers") nanotherapeutics are being devised for targeting of inflammation. Kannan *et al* has been seminal in developing this science translational medicine. She has developed a system to deliver N-acetylcystein which converts into the protective agent glutathione. Dendrimer are rapidly co-localised in activated microphlia in the periventricular region in rabbits with Cerebal Palsy. (Nance *et al*.) These studies have shown great anti-inflammatory effects at multiple points. Studies show restored motor function in animal studies. The group are looking at 2 step therapy – cooling and then anti-inflammatory intervention with nanoparticles. So **nanomedicne** could be the next step for the baby beyond 6 hours post insult. CP and spastic diplegia are most common outcome form in HI. Cortical spinal and thalamocortical tracks - motor and sensory are affected. Researchers have developed an animal model for white matter insult.
In summary asphyxia causing HI in term infants and later CP and related disabilities benefits from cooling therapy. White matter and gray matter injury and inflammation in ischaemia should benefit from dendrimer delivery of anti-inflammatory drugs. The future may also enable cell- based therapy with **glial restricted precursor cells (GRPs)**

Epilepsy
Epilepsy genetics – **precision medicine**: (Ingrid Scheffer) We getting better insight into single gene and multigenes. With precision medicine there will be greater chance for targeted therapy. Medicine for most one-size fits all is now evolved but precision targets the individual differences.
Pathway diseases are illustrated by focal epilepsies. Previously considered structural aetiologies but genes are increasingly being identified eg *DEPDC5, NPRL2, NPRL3* – part of mTOR pathway. Regulates cell development – mTOR. *DEPDC5* – heterogeneity in expression within a family can occur. Scerri *et al* 2015, Baulac *et al* 2015 – showed histological heterogenity in family for different focal cortical dysplasias (FCDI, IIA, IIB). Can also get sporadic germline *DEPC5* FCD and hemimegalencehaly. So numerous genes in the mTor pathway can cause structural disease. Medically mTOR inhibitors can help in this pathway for SEGA size and seizures in patients with TSC. Surgery still has a role as a child can have subtle cortical dysplasia which may be missed and if find mutation need to double check and see if could operate.
Epileptic encephalopathies – pieces of a puzzle can be used to find the syndrome (clinical, electrical, genetic, neuroimaging, co-morbidities etc). Frequent epileptic seizures act that in itself contributes to cognitive impairment beyond underlying aetiology and lead to deterioration with time. This is illustrated in Dravet syndrome where 80% have *SCNIA* mutations. MacTague *et al* Lancet Neurol 2015 provides a great review of the genes implicated to date in the EE group. Developmental encephalopathy however is related to developmental impact which is independent of the EE. Developmental delay may pre-exist the seizure onset, and outcome may be poor even though the seizures stop e.g. *KCNQ, STXBP1*. Overlap with movement disorders occur with various mutations *KCN2, DNM1, STXBP1*.

Phenotypic spectrum of gene e.g. sodium channel – *SCNIA* can be associated with Dravet syndromw, EIMFS (early infantile migrating focal seizures) and small number with GEFS+.
SCNIB is a causative in GEFS+ but is also seen in smaller numbers of Dravet patients.
SCN2A – occurs in Othahara patients, EIMFS and small numbers of GEFS+
Self-limited (benign) infantile onset epilepsies can have a spectrum of presentation.
Understanding the mutation can be important to be clear about optimal management e.g. *SCNIA* – avoid CBZ; whilst *SCN8A, SCN2A* EE may do better with CBZ, Ph and Oxc.
Genetic results can be challenging – it is important to decide if a variant is pathogenic i.e need to decide which is causative. There are population databases which can be accessed to see if the polymorphism is recurrent, pathological and correlates with a phenotype. Need to see if the mutation is de novo or inherited – there is increasing recognition of de novo mutations. About 10% *SCN1A* parents are mosaic. This has implications for counseling – the condition typically appears to be sporadic with unaffected parents but there is increased recurrence risk a parent carries a mosaic mutation. **Mosaicism** occurs everywhere. For *SCN1A* >90% appear to have de novo events but for the 10% who aren't do see recurrence. It may be that the pt or parent is mosaic (e.g. paternal PCDH19). Can quantify percentage of mosaic affected – varies in different cells.**DNM1 encephalopathy** – synaptic vescicles. EE. Need high level coverage of parental alleles to pick up parent mosasicism. Somatic mosaicism leads to brain malformation e.g. double cortex. (Lodato *et al* Science 2015).
Overall genetics of epilepsy is a very exciting field – diagnostic odyssey. Precision medicine based on the genetic pathway is resulting in therapeutic convergence.

Zika virus (Charles Newton)
This is transmitted by Aedes mosquitos – these are vicious day time biters and different mosquitos to the ones that cause spread of malaria virus. About 2.2 billion people are thought to have been exposed. Even in Europe the mosquito has been found.
<u>Routes of transmission</u>
Maternal-fetal – inter-uterine damage, perinatal. Also blood transfusion, sexual but also found in breast milk. The virus was first described in 1947 – from the Zika Forest in Uganda – first cases were reported in 1964 in Uganda with a 'flu like illness. Since then the virus has spread Eastwards across the world. By 2007 there was a Yap island outbreak with an infection rate of 73%, adults were more affected, children had a mild disease. There were no deaths. A further outbreak occurred in French polynesia with a peak in Guillain-Barre Syndrome. It is possible to also get meningoencephalitis and myelitis. Congenital microcephaly however has been the main concern for children, subsequently microcephaly in newborns has been evident 8-9 months after the adult .
Infection in a pregnant woman occurs. Histological features include calcification and more (Mlakar *et al* NEJM 2016. Tang *et al* Cell Stem Cell 2016). The virus affects human progenitor cells.

Evolution – the virus is believed to have originated from Monkeys. Strains associated with neurological disease are from the Asian lineage. There are hypotheses that it was in Africa for so long that inherent immunity was established in Africa. But it looks like disease may have mutated to a more sinister form.

Congenital Zika Syndrome (Vanessa van der Linden.. BMJ 2016;354)

Of 1,883 notified cases, 334 confirmed for congenital infections. 76% reported maternal rash during pregnancy. Clinical signs include

- Redundant scalp skin
- Occipital bone prominence
- Similar pattern seen in other diseases (ie partial destruction of the brain as seen with congenital infections)
- Irritability
- Hyerexcitability - from early on
- The irritability can be less several and can improve in irritability by 3-5 momths
- Can be very hypertonic
- Can have Arthrogyrposis Multiplex Congenita (AMC)
- Reflux oesophagitis
- Exacerbation of primitive reflexes – look as if can crawl and sit – all related to primitive reflexes – ie not volitional. ASTN can be dystonic. Mothers given the false impression that their infants are advanced.
- Epilepsy – seen in 40/127 EEG multifocal polysike – look like spasms but not hypsarrythmia on EEG. Get background slowing.
- Sometimes just have abnormal movements – can be difficult to differentiate from seizures
- Dysphagia - >50% - most comes on by 2-3 months
- Neuroimaging – similar to other congenital infections but there are differences. Calcification especially in cortical and sub-cortical white matter (WM), <u>in the junction of the cortex and subcortex</u>. Also Basal Ganglia, periventricular, brain stem etc involvement. See abnormal cortical development. Brainstem hypoplasia / calcifications, most affected region is the frontal lobe. Some pachygyria, polymicrogyria, herteropia. Basically there is a range of brain malformation affecting cortical development.
- Also can have denervation suggesting anterior horn cell involvement in the patients with AMC.
- Also club foot and hip dysplasia.

Two patients developed hydrocephalus by 3-4 months of age.

Also mild cases are reported with some born with mild microcephaly – CT abnormality are but less marked than in the other cases.

Posturing of the hands and feet.

Some are born with normal HC-then microcephaly becomes evident with growth. Less severe children have extrapyramidal symptoms. Variable tone. Also see macular atrophy with mild retinal mottling, gross pigmental mottling, chorioretinal atrophy, optic disc pallor. Posterior pole macular atrophy – this distribution is different to other congenital infections. 2 had patients had glaucoma. Audiology – 25% have bilateral abnormalities indicating hearing loss.

Current guidelines for clinical practice. Helen Cross –
WHO recommended measuring HC in the first 24 hours. All mothers should be asked about clinical signs and symptoms suggestive of Zika infections, and or lab confirmation of Zika infection in pregnancy including when possible infection occurred ie first, mid or final trimester.
Neonates should be examined to assess whether the head appears disproportionately small relative to the face or body.
In neontates with congenital microcephaly or where head disproportionately small relative to the face or body a full neurological, visual and hearing assessment is needed.
If this found and other explanations are not known the neuroimaging is needed.
Where the findings are borderline it is still important to see if there is evidence to support the diagnosis.
Where microcephaly is definite need MRI.
In some setting might have to do US of head but this is not ideal as there is a very small fontanelle window with limits views.
Where cong microcephaly / disproportionate face to head size/ Zika suspected – it is still necessary to test for all congenital infections as there are a number of cases of dual infection. But also do need Zika testing to gain specificity.
Management – inform families and advise, supportive therapy, multidisciplinary therapies, counseling
Follow-up – need to watch for longer – prepare for further complications which come out with time. Look for complications that put the infant at risk – eg swallowing. Psychological well being important.

Epilepsy surgery (Kees Braun)
For focal seizures – even with interictal generalised activity and contralateral side epileptic discharges there is still a 63-80% seizure resolution with surgery where there is a clear MRI focus.
7T MRI can show lesions in MRI negative cases. Also need an expert to review these scans.
Also 9% of lesions are not relevant for the epilepsies; 3% of idiopathic epilepsies have coincidental MRI finding. 4-50% of MCD are MRI negative
Challenges for surgery in genetic epilepsies e.g. DEPDC5 mutations
Aim is not only seizure freedom but need to help with developmental delay and cognitive outcome as well.
Found parental education was a major predictor for outcome.
Early surgery and medication withdrawal were better predictors for outcome.
So may have child with non-eloquent area lesion which may be controllable with AEDs but actually surgery may **cure** them and remove the need for AEDs.
Do children need to have seizures to qualify for epilepsy surgery? Possible to have subclinical PLED like activity – surgery can improve cognition in these cases.
Outcomes: Depends on measure used e.g. Engel or ILAE, also duration of follow-up. Influencers for outcome – experience, duration of follow-up (most sz improve with time), underlying risk factors for recurrence – duration sz >5yrs, normal MRI etc.
Longterm success – limited data. At 5 yrs post surgery – 57% Engle 1A

Post withdrawal of AEDs - Sz recurrence risk lower in the post-surg group and children do better than adults.
If recurrence occurs – still 75% chance of regaining control – ie little evidence to support worry that after relapse at risk of not being able to regain control. Basically just unmasks ongoing underlying seizures activity.
When to withdraw AEDs post surgery? Wide differences worldwide. UCLA prefer a cautious approach, Netherlands happy with earlier withdrawal. Boshuisen *et al* Lancet Neurol 2012. Early withdrawal slightly increased the risk of relapse. Biased data as the later you start your AED withdrawal the longer you have control! Basically just unmasks seizure failure earlier. But there is data to support that early withdrawal fas cognitive benefits , the earlier AED withdrawal ocucred the IQ was significantly higher as well as the change in IQ.
Surgery is increasing in children - Aetiology – MCD, tumours, HS
Good support for earlier surgery being better. Should consider in generalised epilepsies if ep surg could help - provided MRI consistent with lesion.
Long-term sz freedom can occur in 60%
Early withdrawal not unsafe and may improve cognition.

Ketogenic diet: Eric Kossoff
Access to the diet has become a worldwide resource – adapted to different cultures. There is now lots of data. Review in the Cochrane paper and ILAE statement for use / role has been very helpful. Lots of supplements coming in VitD, multivits but lots more.
Persisting controversies –
<u>How strict</u> – no fasting, no admission, gradual introduction - all reviewed with OK outcomes. Not set – any can work.
<u>4 different KD versions</u> – standard American diet, KD, MCT diet, modified Atkins, low glycaemic index treatment – actually all viable
<u>Diet in a pill?</u> Under research – but not there yet

Arthryogryposis multiplex congenital (Hanok Toplgu)
Non-progressive contractures from birth, can resolve with physiotherapy
There are multiple causes for decreased fetal movements – ie multiple differentials
Genetic causes include distal arthrogryposis. Fetal or neonatal akinesia / hypokinesia or fetal akinesia deformation sequence (FADS). LMN disease, lethal congenital contracture syndrome (Finland); lethal arthro with ahc (mainly Finland)
Amyoplaisia this is not a genetic, developmental disorder. It may be regional e.g. lower limbs only
Form of arthyrogrposis. Have fatty-fibrous replacement of muscle, internal rotation of shoulders, extended elbows, ulnar deviation - pronation (Hall, J 2014 – good review). Perinatal US detects only in 25% of cases.

Amyoplasia	*versus*	*others (can use to diff in the clinic setting)*
Alert	versus	lethargic
Spared & mobile trunk	versus	scoliosis
Dimples, nevus	versus	not

Approach to assessment
Divide up: Involvement of limbs only; Limbs and other systems; Neuromuscular

Logic: Collagen response – lack of joint movement, thickening of joint capsule and surrounding capsule etc
Distal arthrogryposis: Distal parts but 50% due to contractile proteins of skeletal muscle e.g. MYH3 etc
Fetal akinesia deformation sequence (FADS) severe form - Pulmonary hypolasis, Intraunterine Growth Retardation, fracture, brain disorders
Severe forms of arthrogrypsis: SMA, cong Myotonic Dystrohy, cong myopathy, cong MD, early onset neuropathy, brain dis.
Affects 1 in 3000 live births

Red flags

- FH+ve
- Decreased fetal movements
- Oligo/polyhydramnios
- Maternal illness
- Parental age
- Decreased spontaneous movements
- Hip dislocation
- Arthrogryposis

Natural history
AMC with CNS involvement has an up to 50% mortality
Whilst survival for amyoplaisa at 20 yrs is reported in 94%

Causes – from 2000 gene studies denote various myogenic and NMJ aetiologies – especially for distal forms. E.g. *CHRNG* and *RASPYN* mutations
Fetal akinesia: Escobar syndrome – form of myasthenia –occurs with *CHRNG,* also *CHRND* and even *RYR1* mutations.
Management - growth, feeding, ambulatory support, airway etc
ie multidisciplinary
Pena-Shokeir syndrome – typical phenotype can detect antenatally
Amyoplasia – despite disabilities can lead fairly normal life.
Molecular studies
Laing N, 2011 – more than 200 mutations points linked with fetal akinesia-neuromuscular (Ravenscroft G , 2015) – improved genetic diagnosis leading to better phenotypic expression. Using NGS for 48 families with predominantly distal contractures she found mainly muscle genes in the 20 who gained closure.
Multiple contracture, mainly distal seen with Ullich disease

Congenital myasthenic syndromes

Most AR, only slow channel AD
Clues / workup

- History fluctuating weakness – better after rest / sleep.
- Exercise intolerance
- Repetitive stimulation test – 3 Hz – after rest and exercise
- Single fibre- EMG (tricky under 10 yrs of lfe)
- Rarely do edrophonium test – limited outcomes – do in ICU with atropine and know what to watch for.

- Genetic analysis – direct gene anylsis or NGS – need good phenotype to direct screening
- Morphological – biopsy – not for CMG but for differentials useful – overlap mutations e.g. may have high CK, and LGMD, structural myopathies
- Antibodies (AChR-, MuSK-, Titin, LRP4 antibodies)
- Pathology – thymus gland ? (CXray, CT, MRI)
- EEG, MRI (can have cognitive impairment)

Treatments – often relate to specific subtypes

- Pyridostigmine
- 3,4-diaminopyridine (occasional add on treatment with pyridostigmine)
- ephedrine (some sub-types)
- salbutamol, albut
- fluoxetine
- etc

Genes
Most are postsynaptic (huge long list)
Presynaptic – *CHAT, SNAPSB, Synaptogein 2*
Synaptic / basal maina – *COLQ; LAMININbeta2*
Postsynaptic – massive list

CHAT mutations
Have reduced fetal movement, recurrent apnoea in infancy, deteriorate following birth and are typically ventilated, especially with febrile illnesses. Improved with time but ongoing motor delay. Limb girdle distribution of muscle weakness persists

COLQ mutations
Neonatal onset – ptosis, external ophthalmoplegia, recurrent apnoea, respiratory insufficiency, reduced pupillary light reflex, repetitive stimulation motor action potentials (MAP) get a double CMAP (compound MAP).
Pyridostignine can worsen the condition so should be avoided. Treatment can be possible with ephedrine with some improvement reported, otherwise main stay of care is tracheostomy, and support for WC dependency and psychomotor delay.

CHRNE mutations
Consangeous family i.e AR
Onset in first year of life
Positive response to AChE-inhibitors
Constant proximal weakness and exercise intolerance

CHRND mutations
Onset 1st year life
Motor / developmental delay; exercise intolerance

RAPSYN mutations
Onset prenatal / neonatal, AMC, crisis with deterioration, ptosis, no pathological decrement in most, responds to pyridostigmine, complete recovery

DOK7 mutations

Manifestation in infancy, limb-girdle weakness. Waddling and lordotic gait with internally rotated legs, fluctuating symptoms for weeks, pathological decrement only once (ie intermittent). Rx ephedrine. Important differential diagnosis for congenital myopathies.

GFPT1 mutations
Limb-girdle weakness, no ophthalmoplegia, no ptosis, benefit from esterase inhibitors, no mutations in *DOK7*

Duchenne session
Ros Quinlivan
Before 1990 – mean death was by about 18 years of age usually related to respiratory complication. By 2002 boys were living to 35 yrs (mean 28yrs) and some even older.
Recommendations by the Lancet Neurol guidelines and the Cochrane review for steroids have helped guide multidisciplinary care. Steroids prolong walking and cut the scoliosis risk from 90% to 10%. Ricotti *et al* 2013 JNNP – looked at steroids regimens. Those who started less than 5 years of age doing better therefore supports early treatment
Ataluren registered FDA and approved by NICE
40mg/kg/day – over 3 divided doses (come in 125, 250, 1000mg sachets) orally
Used 6 MWD to track progress.
Do annual cholesterol and TG, U&E, LFT, FBC, cystatin C (for renal function as creatine low with DMD so can't be used as measure)
Recommendation – need to identify patients with nonsense mutations to identify those eligible for ataluren treatment. Cost euro300 000 per year. Not yet registered in SA.

Sylvie Tuffery-Giraud
Deletions account for 60-80% patients with DMD and duplications for 6-10%. So most screens review deletions first – usually look for 18 common exon deletion regions especially exon 45-48 which detects up to 98% of deletions. But this method can't detect duplications. Large rearrangements detections occur via MLPA, array CGH and NGS.
aCGH – full spectrum of large rearrangements – triplicates, complex rearrangements (<1% mutations, intronic boundaries, dup – BUT can't tell you where location)
NGS – can detect deletion and duplications
MLPA still most commonly used technique and very efficient but pitfalls e.g. is single exon deletions – can give false positive. Also false negative e.g. deletion outside probes or wrong extent of deletion
DMD cases made up of 26% point mutations – 48% of these are nonsense mutations (less so for BMD 13%)
Abbs *et al* Neuromuscular disorders – guidelines report
Typically sporadic but mother may still carrier (up to 30%) – important for antenatal counseling Collaboration is happened with the French lab and the PTC group.
Mean age of diagnosis 4.3 years when no FH (van Ruiten *et al* 2014 ARCHs) – need to improve on this.

Deletions antisense-mediated exon skipping to restore an open reading frame – shorter partially functioning protein.
Need to encourage development of registries. In France there are over 3000 pts documented in the registry representing most of the affecteds in France and based on this they can be rapidly identifed if eligible for trials.
Getting point mutations assessed can be challenging – hoping will become more viable with NGS.

Eugenio Mercuri

Outcome measures for DMD trials

6MWT measures pt endurance, while TFTs (e.g. 10m wlk/ run test) measure burst activity. Both are complimentary. North Star Ambulatory assessment measures global ambulatory status using 17 items – available on-line.
Need more then the 6MWT. Generally a cut off at 350m is used as a marker for the stage of decline.
Children above 400m are likely to remain stable over the next 1 year. Below 400m – some decline over the year as part of the natural history of condition. As such the natural history of DMD is likely to bias the results of some of the interventional studies. Children in the under 300m have higher MRS fat fraction which indicates precipitous loss of ambulation. Many of the previous studies are compromised by not taking these factors into account. Ataluren is a read-through agent. It has high specificity for premature stop codons without termination at the usual stop codon and permits translation of mRNA and the re-production of dystrophin.
Bushby *et al* Muscle nerve 2014 reported one of the earliest studies. There was different inclusion criteria to what would be used now. There was a well tolerated phase 2b study. The difference between 40mg/kg/day and placebo was that they gained 30m difference. Similar tendencies with other markers – the treatment group did do better but the effect appeared small.
So the researchers decided that if focused on the group about to have decline the effect was much more impressive. When this was demonstrated – lead to the approval. Hans M *et al* Neuromuscular Disord 2015.
This exercise has increased the understanding of the natural history of the condition.
So for the current assessment there is a different study design
Inclusion criteria

- >7-16 yrs
- Steroids >6mths
- 6MWD >150m and <80% predicted for age and height
- prespecified analyses

n=115
>300-400m subgroup underwent meta- analysis
and control group
Found improvement with the intervention arm. The >300-400m – the difference much more marked – at 48 week end point. Found no major AE. So the difference in the whole population was small – but when the key subgroup population were reviewed the outcome much better.
Now looking at meta-analysis to compare data from all studies.

Charles Newton:
Update on HIV neuro in children

Good maps/graphs on burden of disease and DALY's (especially SA a key area)
Factors associated with CNS involvement
Maternal factors
Route of transmission
Patient factors

Genetic propensity
Apoliprotein B particuarly important

Range of neurological complications broad
Predictors of HIVE development (includes high immune activiation –ie low CD4 count)

TBM in HIV infections:
Imaging findings less obvious
Use of steroids: role less clear in HIV infected individuals that in uninfected where they are recommended.

Cerebrovascular disease, probably more common than is recognised
ADEM also described
Neoplasms: being seen more commonly in resource
Seizures. Nb references, Ngugi et al, Lancet 2013; Samia JCN 2013, Bearden JAIDS, Birbeck et al, epilepsia 2012 (interactions between ARV's and AEDS)

ARV's
Certain drugs have better penetration
Effects of ART on the developing brain

Possibilities for the future:
HIV still a considerable burden
Neuro manefestations diverse
ART has had significant impact, but interactions and side effects problematic.

Neurocystercicosis
Prof Pratiba Singhi

Overview of the range of clinical and radiological presentations for neurocystercicosis
MRS can be helpful in differentiating NCC vs tuberculoma (has lipid and choline peak)
Antigen detection

Management:
Cystercidal medication (albendazole), steroids

Factors to be considered
Anatomical location of the cyst
Size
Other factors

Albendazole effective against meningeal and parenchymal forms
28 days (at least 7 days for single lesion). 15 mg/kg/day

Absolute indications for steroids:
multiple parenchymal lesions
also AEDs (CMZ most commonly used)
(1 year of treatment after the resolution of the cysts seems to be adequate).
Prolonged AEDs may be needed in calcified lesions.
Neurosurgical interventions only for intraventricular lesions which may be causing hydrocephalus.

Community inteventions to reduce endemic tapeworm, can reduce epilepsy in endemic areas by approximately a third!

Training symposium
Paul Larson
University of Nebraska
Open resource tools on the practical neurological exam

Can use to design integrated approaches to applications: eg the LP (anatomical overview, demonstration of the procedure, review CSF analysis)

Also developing brief tutorials on specific conditions looking at the underlying anatomy and pathophysiology, assessment and management. "Flipped classroom" expected to be familiar with the concepts prior to the tutorial.

Use animation which is engaging and entertaining, testing along the way

Principles of good instructional design
Analysis, strategy, evaluation
Design teaching tools that meet your needs
Design so others can repurpose content for their needs
Make as interactive as possible

Can ask the students to go through the website material and then in tutorial show novel material and ask students to apply the principles.

Try to get technical help to desgn material that is not going to be absolete quickly, that can be accessed by many people

Dr Christen
Interprofessional postgrad paed training

Canmeds framework: 7 overlapping competencies
Feedback and workplace based assessments can be useful
MiniCEX (observation, documentation and feedback immediately afterwards)

Tuesday 3/5/2016
Jo Wilmshurst (plenary)
Threats to child's brain in resource poor country

Environment
Genetics
Direct aquired conditions
Maternal mental health
Nb poor access to obstetric care
Ref infant mortality figures in different

Genetic influences different, unknown

Epilepsy and treatment gap both in terms of acute convulsive status as well as regular antiepileptics
Specific viral infections, both congenital forms as well as direct CNS and autoimmune responses

HIV
Overview of changing spectrum of neurological effects in t he post ART era

Measles
SSPE

Bacterial infections/meningitis
Parasitic infections

Diagnostics and interventions
Stigma
Training
APFP principle

Cerebellum-cognitive effects
What is known about cognitive affective syndrome in children?
Problems with executive function, generally better verbal than non-verbal performance

Malformations of vermis seem to involve affective and social disorders (even ASD type symptomatology)
Hemispheres: more EF, visuospatial, linguistic abilities

Developmental dyslexia also associated with cerebellar abnormalities: often having mild motor problems (balance, "clumsy" other visuospatial etc), nb link to language hemisphere

Cerebellar Cognitive affective syndrome (CCAS)
Problem solving (failure to organise visuo-spatial material)
Memory
Linguistic
….

Cerebellar mutism:
Often occurs after resection of large cerebellar tumours
Risk factors: tumour type (medullobl)
Tumour size, midline location, brainstem involvement

Functional topography of human cerebro-cerebellar connections:
Eg frontal lobes linked to vermis
Nb ref Stoodley et al, cerebellum 2016; 15: 34-7
Cerebellum is important for procedurally learning…
Especially nb in early childhood

Screen time: threat to children's brain's (screen dependency disorders)
Aric Sigman (plenary)
Criteria for DSM V
Preoccupation
Withdrawal symptoms
Increasing tolerance
Failure to reduce or stop
V similar to other addictions basically

Not seen to be purely secondary to other disorders (anxiety and depression)

Risk factors for screen addiction:
Age
Exposure (average dose)
Type of activity
Pre-existing psych condition
Neurogenetic vulnerability
Neuroepigentic chnages

Recommendations of only 2 hours outside of school work per day (American health department)

screen dependency disorders and neurologial disfunction: there is a correlation, but precondition vs outcome or bidirectional?

Addiction:
Involves impaired reward processing
Impaired impulse control
Neural correlates: amygdala, nucleus imcumbens…
Appears to be alteration of the dopaminergic system as a result of gaming

Transition to dependency:
It is a spectrum with levels of severity
Yuan et al, 2011 PlosOne: multiple GM and white matter microstructural differences in those with gaming disorders
Lin F et al, 2012 Plos One: similar regions to other additctions
In review, the pattern seems to be brain regions which are involved in cognitive control and reward systems,
Striatal area a hotspot

Early screen environment: strong links with parental role modelling
May result in high levels of screen time and increased risk of screen dependency
Physical activity protects against screen dependency
Link of conflict of interest with e-learning and gaming…
Principle of precaution

ADC: leading article: time for a view on screen time (Sigman)
"sugary diet" analogy
can be harmful and "educational" at the same time (vitamin D analogy)
screen exposure under 2 is particularly problematic
bottom line is that amount matters, age at starting matters and content also matters

Plenary 2:
Anna Jansen
J Stobo Pritchard award
Developmental brain malformations: genes and pathways

Barkovitch classifications useful:
1. Malformations secondary to abnormal neuronal and glial proliferation or apoptosis
2. Malformations do to migrational disorders
3. …

Highlighted the importance of careful clinical neurological examination and pattern recognition both in terms of clinical malformation patterns as well as MRI features.

Array CGH
Targeted gene sequencing

Whole genome exome sequencing
Looking at relatively well understood conditions such as TSc to elucidate mechanisms

neonatal seizures
G Boylan

Seizure burden seems to have reduced in those who are cooled, but more with moderate than with severe HIE. Medications not only reduce the actual seizures, but also reduce clinical signs. Difficult clinically

aEEG can be useful, but need experienced users. Can screen and then select those who need more detailed monitoring

now there is a automated EEG tool which generates a seizure porbability output.
Validated against 3 expert clinical raters
Performed really well
The agreement is high with the longer seizures which are more important in the real world
Alarm generates a signal for someone to come and look at the baby
Has been published in 2016.

Management
Pb still firstline
Second line still varies hugely between centres
Ref Glass et al J Pediatr, 2016

Levitiracetam second line, lidocaine,

ESES symposium
Jansen
CSWS is the EEG pattern
ESES is the electroclinical syndrome which includes CSWS for at least 50-85% of sleep and cognitive regression

Genetics:
J Lemke
Onset a few months to 12 years, but peak 4-5 years
15-18% have cortical malformations of cortical development
clinical epilepsy can be multiple different seizure types

30% cases had IFE before
15% have family history of ESES/BECTS

Aetiology
MECP2: 20% of Rett's girls. But usually clear clinically
CNV's 10% of cases have CNV's on chr, 4,8,9, 15,16, X
What does this teach us? GRIN2A highly associated
17.5% of those with ESES associated with GRIN2A mutations (lower with the less severe phenotypes)
codes for an ion channel: hippocampus and cortex is where 2A mainly expressed

GRIN2A
DD/ID and normal to severe speech delay
Very monotonous speech, short vowels
Epilepsy: ESES/CSWS/LKS
Muscular hypotonia
May have movement disorder
May have visual abnormalities (mild-severe)
MRI findings may be non-specific

Mutations tend to result in gain of function with channel overstimulated
6 or 7 mutations
? treatment of NMDA receptor gain of function: Memantine
this is only reported in one patient.

KCNA2 also described (voltage gated Potassium channel), though clinically weren't typical of the syndrome

Take home:
GRIN2A, MECP2 are clearly associated
KCNA2 possibly
Remember CNV diagnostics
Personalised medicine may be possible in a small number of selected cases.

Next 2 years – Ingrid Tein
Highlighted the role of NGS and the capacity of greater understanding of the pathogenesis of mutations – understanding the functional implications – leading to better outcomes – **PRECISION** medicine.
Need good RCT to assess the efficacy of interventions. Need more collaborations
Intellectual disability – field expanded significantly
Epilepsy- in the field with EE expanding – predict the genes based on temporal pattern of expression, terms more via gene and expression e.g. *STXBP1*.
Increased understanding immune-expression in epilepsies
Precision medication illustrated by role of *KCNT1* – gain of function mutations
Novel therapeutics
– mananine – GRIN2A – NMDA receptor antagonists
Nanotherapies
Stem cells:
Gene therapy – opticogenetics; allele-specific RNA specific therapeutics
Novel diagnostics:

Expansion of non-invasive screening – cEEG, MEG, PET etc
WES – amplication of genetic hetererogeity >22,000 variants – better understanding
WGS
Epilepsy modeling – animal or human derived stem cells – intrauterine therapy in the future?
Neuroprotective therapy _ Fatemi *et al*
Technique using nanotherpay – delivery anti-inflammatory drugs to the brain. The dendrimer can cross the BBB, get into the cell, cleave with and release in the cell. Leads to inhibition of key agents. Targeted therapy to arrest damage and this system could work of other neurodegenerative conditions.
Neonatal neurology – promotion of brain development – need to promote nutrition and pain management.
Zika virus - global worldwide neurotropc virus.
Migraine therapy – new FDA approved – cerena transcranial magnetic stimulator – prevent or use as therapy. CGRP antagonists – calcitonin gene-related peptide for migraine – adult studies under way.
Neuroimmunolology – Grans *et al* – autoimmune encephalitis Lanct Neurol 2016 – first guidelines and definition for the field. Great flow charts
Therapeutics – first oral agent for MS – fingolimod – data should be out on this in the next 2 years.
Getting better understanding of phenotype of autoimmune encephalitis group. Immunophenotyping important is important.
Arterial ischaemic stroke – depends on the age of onset. Relates to plasticity.
Synaptigenetics – peaks at 4 years and plateaus by 10 years. Reflects cortical development – get thinning of cortical mantel (Kirton *et al* 2016 neurology – the plastics champs trial: class 11 study)
Imaging mechanisms of plasticity – DTI is important in assessing
Vascular effects of infection in early stroke, main triggers are URTI, GE then OM with herpes found in many. For pediatric embolectomy must have a stroke team – small infarct within 6 hours where TPA has failed.
Movement disorders: Genotype is not the final answer. E.g. *ATP1A3* – range of phenotypes seen. New therapies seen with improved meds - relates to subtype specific anti-muscarininc meds; vesicular dopamine uptake inhibitors; DBS also specifically for good selected pts (e.g. DYT1 mutations). New diseases – delineation of secondary neurotransmitter disorders where CSF profile does not fit a known neurotransmitter disease. Disorders of serotonin deficiency. Identification of CSF neurotransmitter patterns, using novel mechanism of induced pluripotent stem cells – CRISPR technology.
Novel therapies using a adenovirus vector for Neuromuscular disease: Helped by involvement of Treat-NMD. CRISPR gene editing for DMD mice. Zebra fish models etc.
Novel therapies
SMA – intrathecal ASON therapy – converted type 1 to 2
DMD similar progress – Hoffman *et al* 2012 VBP15 – developing a steroid agent without the side effects

Neurometabolics - >100 subtypes of CGD
Widening the field +++

Cong disorders of autophagy – emerging in the field of neurodegenerative and neurometabolic disease
Novel treatments guided by precision medicine. In uterine therapy e.g. serine deficiency. Novel in vitro fertilization genetics therapies.

Future pharmacologic therapies

- Mitobiogenetics
- Mito dynamics
- Mitophagy
- Unfolded protein response

Need high quality RCTs

- Lots of data to restore mitochondrial function: EPI-743 in Leigh syndrome
- Up-down cycle ergometry and 31P-MR spectroscopy
- 3 parent embryo

Rodan *et al* Mitochondrion 2015: 22:66-74
Mitochondria and Stemness and Differentiation – mitochondria can disrupt pluripotent function of stem cells.

Neuropyschiatry – Casey *et al* 2015 Neuron. Treating the *Developing* rather than the *Developed* brain. Shows these waves / peaks of window there are age matched time windows when damage / risk greater and robustness more marked. E.g. inhibitor neurotransmission peaks early in the amygdala. Increased in prefrontal cortex is during adolescence.
Autism – novel mechanisms leading to future therapies
ASD and cortical projection of neurons is found in deep prefrontal with all 9 autism associated genes
Targeted therpaies – Topoisomerases – agents to impair function and Microbiotica have major implications (Hsaio *et al*)
Treatable aetiologies – folic acid; TSC – mTOR; Neurooncology – personalised medicine; Lasar interstitial tumours; Robotics in neurosurgery – tumours, lesions and CP.
Stem cell therapy –(Fatt *et al* Stem Cell Reports 2015) -role of **metformin** – Dadwal *et al* Stem cell reports 2015. Leads to improvement of motor function in mice with HIE.

Bernard Dan – **ethics in neurology**
Supported the need for RCT – need evidence-based medicine
Evidence-informed medicine.
Ethics is part of good practice

- Respect and trust
- Tension between identity and difference
- Empathic experience of otherness
- (not definitive) – resolution with humility

observed signs, facts, empirical data – incomplete knowledge, conjecture, situational judgement.
Decision-making inscribed in time – priorities, postpone difficult questions not understanding too quickly"

Clinical encounters, narratives situations, singular truths, multiple realities, not to expect to coincide

Neuromuscular session: DMD
6 minute walk test – younger children seem to show improvement – need to watch for longer – large variablility.
Ataluren confirmatory trial in DMD (Ros)
10-15% nonsense mutation – premature stop codon. Approved trial for European area, Israel and S Korea.
Inclusion criteria:
>7 and <16yrs
able to walk >150m
<80% predicted for age and ht
Study looked at ADLs – phase 3 trial over 48 weeks. Study group better outcomes. Pointed out that stabilization as important as improvement as the condition is degenerative

North Star (Francesco)
Ataluren – pending universal approval – some areas have it others still waiting.
General feeling – effective treatment and should be given to viable patients.

Eteptlisen (E Mercuri) – under review FDA- for exon 51 skipping (13%) of DMD.
24 week phase b then open label extenson – 201/202 study.
201 - % dystrophin positive fibres
202 – 6MWT
Supportive from Norht Star and other markers
N=12 4 year follow up
By 2015 n=114 exposures – 88 pts at 30mg/kg or higher. 4-19 yrs of age.
No major SE
SE – headache, proteinuria, dizziness etc
Some erythema at the infusion point.
Otherwise seemed very safe.
Adjusted methods for quantitating muscle tissue. All 3 mthods showed an increase in muscle dystrophin.
Need to know if enough to improve function.
Efficacy – lack of placebo control led to search for comparative DMD natural history. Looked at 12 external DMD databases – extensive clinical data.
For the controls recruited from databases. All had to be on steroids, >7 yrs and exon 51 ameniable. Identified n=13 children for comparison to n=12 on treatment.
Results – little difference in to and control. May reflect need for build-up to get functional effect. With time the 6MWT gap in the 2 groups becomes more spread out.
All the external controls had lost ambulation by 4 years of study – typical for exon 51 deletions. Treatment group showed that all except 1 were still walking at 4 years for the intervention group. Bello et al Neurology in press
Ability to rise independently over time – similar outcomes
First therapeutic study to show good support for therapy – main issue is the impact on preserved ambulation.

Adaption for the 6 min walk test (Natalie Goemans) 6MWT is the main stay for study outcomes. Looked at longitudinal data. N=191 follow up intervals from n=58 pts.
Mean age 9.4 yrs
Used multivariable linear regression to analyse data e.g. age etc
Age was an important factor
In second assessment – ability to climb stairs was very important and ability to raise from floor.
Identified 4 groups – fast decline, moderate decline, stable, improved.
Death and DMD – some worrying data suggesting possible adrenal insufficiency
Overall life expectancy improving. Most die from combined cardiorespiratory causes but 1 in 5 died younger and unexpectedly. Need to watch more adrenal insufficiency and intercurrent infections and missed OPDs.
Highlighted the role of a care coordinator.

Myasthenia gravis (Garg, India)
Neonatal
Congenital
Juvenile / autoimmune
Retrospective overview.