International League Against Epilepsy Leadership Course and International Epilepsy Congress 2023 report
– prepared by Dr Serini Murugasen (Paediatric Neurology Senior Registrar)

Overview

I was fortunate to be selected for the International League Against Epilepsy (ILAE) Leadership Course following nomination by the Africa Chapter of the ILAE. The course was held over 2 days in Dublin, Ireland and immediately preceded the International Epilepsy Congress 2023 (IEC2023) organised jointly by the ILAE and International Bureau for Epilepsy (IBE). As part of the bursary, my attendance at the leadership course and registration for the Congress were covered, and the remainder was through support from the Department of Paediatric Neurology, so I was able to make the most of this trip in terms of both personal and professional development.

International League Against Epilepsy Leadership Course, 1-2 September 2023

Thirty-two members of the ILAE from all represented regions were selected for a two-day leadership course designed to give an overview of the ILAE and prepare the individuals to assume senior positions in their respective chapters/fields. Organisational content covered included the history, structure, vision and mission of the ILAE, and its partnership with advocacy group the IBE. Professional development content included strategic and financial planning, communications, conflict resolution and negotiation, finding work-life balance and a dedicated session to finding and developing your personal leadership style. The second day of the course also involved active engagement with the ILAE General Assembly and Global Chapter Convention. It was an excellent and comprehensive leadership course that provided good networking opportunities with other professionals in the field of epilepsy from around the world. The formal programme ran from 8am until 6pm and there were events at 7pm on both days allowing for further exposure to senior members of the ILAE.

Day 1: Friday 1 September

SESSION	TIME	SPEAKERS
Welcome and Opening Remarks Video Introductions	08.00-08.10 08.10-08.40	Jaideep Kapur and Reetta Kälviäinen
ILAE Vision and Organizational Structure	08.40-09.20	J. Helen Cross
Coffee Break – Foyer, level 2	09.20-09.40	
Chapter Leadership and Management	09.40-10.20	Reetta Kälviäinen
Strategic and Financial Planning Workshop (Interactive)	10.20-11.50	Julie Hall and Linda Beza
Merits of Publication and How to Do It	11.50-12.30	Stéphane Auvin
Lunch with ILAE Leadership – Foyer, level 2	12.30-13.45	
Communications (Interactive)	13.45-14.45	Julie Hall and Nancy Volkers
Conflict Resolution and Negotiation	14.45-15.45	Jaideep Kapur
Coffee Break – Foyer, level 2	15.45-16.00	
Finding Work/Life Balance and Preventing Burnout	16.00-16.40	Ingrid Scheffer (Sheryl Haut to present course introduction via Zoom)
Patient Public Involvement and IBE/ILAE Partnership; Achieving IGAP	16.40-17.20	Francesca Sofia
Wrap-up of the day and preparation for the following day (Incl Congress Programme)	17.20-17:45	Jaideep Kapur and Reetta Kälviäinen
Joint ILAE Mentoring and Leadership Reception – Foyer, level 5	19.00 onwards	

Day 2: Saturday 2 September

SESSION	TIME	SPEAKERS
Welcome	08.00-08.05	Jaideep Kapur and/or Reetta Kälviäinen
Leadership Throughout History: Why Do We Need Leaders Today?	08.05-08.45	Peter Wolf
How to Run an Effective Meeting (Interactive)	08:45-09:25	Solomon L. Moshé
How to Get Involved in the ILAE Young Epilepsy Section	09:25-09:55	Johann Sebastián Ortiz De la Rosa
ILAE Global Chapter Convention – Wicklow Hall 2, level 2	10:00-12:00	ILAE Leadership
ILAE General Assembly – Wicklow Hall 2, level 2	12:00-13:00	ILAE Leadership
Lunch with Chapter Leadership – Foyer, level 2	13:00-14:00	
Your Personal Leadership Style: Assessing and Leveraging your Strengths and Understanding your Weaknesses (*There will be a coffee break during this session*)	14.00-17:00	Tom Armstrong
Wrap up and Evaluations	17.00-17.30	Jaideep Kapur and Reetta Kälviäinen
Presentation of Certificates	17.30-17.45	J. Helen Cross
IEC Welcome Ceremony and Reception – Auditorium, level 3	18.45 onwards	

International Epilepsy Congress, 2-6 September 2023

The IEC2023 was held 2-6 September in the same venue and followed immediately on from the ILAE leadership course. Content was varied and included a mixture of platform sessions, symposia (industry and non-industry), teaching sessions and the presidential symposium. There was also an exhibition hall for poster presentations and members of industry to exhibit. The daily formal programme ran from 8am to 7pm most days with the exception of Wednesday when the congress closed at 2pm. It was a very busy schedule with multiple sessions running concurrently, and often equally interesting and relevant content presented in two separate concurrent sessions. Where possible, I prioritised attending sessions relevant to paediatric neurology and resource-constrained settings. I have listed below all sessions from the congress that I attended. I have summarised the content of the sessions I found most useful and relevant to our context here in South Africa, as there were a few instances in which the diagnostics and therapeutics discussed were well beyond what we could offer and most of the content – while interesting – was not likely to be accessible to our population in the near future. I used the afternoon between sessions to speak to various exhibitors about possible research and clinical collaboration in Africa, and to promote and encourage attendance at the International Child Neurology Congress 2024 to be held in Cape Town.

Teaching sessions attended were “Epileptic encephalopathies” (3/9/23), video session on neonatal and paediatric epilepsy cases (4/9/23) and “MOGHE (mild malformation of cortical development with oligodendroglial hyperplasia in epilepsy): a new underdiagnosed epileptic brain lesion” (5/9/23). These sessions were purely educational and did not extend to significant new concepts or content in these fields – as such they are not reported in detail in this report.

Friday 1 September	**Saturday 2 September**	**Sunday 3 September**	**Monday 4 September**	**Tuesday 5 September**	**Wednesday 6 September**
8am-7pm ILAE Leadership Course	8am-7pm ILAE Leadership Course 7pm-8pm IEC2023 Welcome Ceremony	8am-9.30am Epileptic encephalopathies	8am-9.30am Video session on neonatal and paediatric epilepsy cases	8am-9.30am Immunity, inflammation and epilepsy	Morning – spent networking and promoting ICNC 2024
		9.45am-11:45am Defining meaningful outcomes in the genomic era	9.30am-11.30am Newly diagnosed epilepsy: identification and intervention of neuropsychological sequelae	9.30am-11.30am Complex and rare epilepsies: The past, present and future	
		12pm-1.30pm Reducing the treatment gap and mitigating economic implications in paediatric epilepsy	12pm-1.30pm The ILAE syndrome classification as a roadmap for epilepsy-associated co-morbidities	12pm-1.30pm Identifying and managing neurobehavioural comorbidities in children with epilepsy – can we bridge the gap?	Departure at 11.30 for airport for return flight.
		5pm-6.30pm Neonatal seizures and epilepsy – From the past to the future: why we still have controversies?	5pm-6.30pm Hypothalamic hamartoma – evolving understanding of evolution and treatment of an epileptic syndrome	2.15-4.15pm Congress-organised walking tour along River Liffey	
				5-6.30pm MOGHE (mild malformation of cortical development with oligodendroglial hyperplasia in epilepsy): a new underdiagnosed epileptic brain lesion	

IEC 2023: Sunday 3 September 2023

Defining meaningful outcomes in the genomic era.

1. **Talk 1: Opening talk by the mother of a child with a genetic DEE (SLC6A1).**
   Personal journey from noticing motor stereotypies and developmental delay through the diagnostic process and moving into advocacy. SLC6A1 Connect has hosted scientific symposia. Primarily driven by the need for treatment for this condition. Importance of QOL rather than seizure-related outcomes when it comes to making a difference to patients.

2. **Talk 2: Are all outcomes relevant in the clinical setting?**
   Change in what outcome are measure over time e.g. seizure frequency, side-effects and treatment-related toxicity. Now in addition to these we look at health-related QOL including impact on schooling. Impact on the EPIC study on the landscape of epilepsy-related research and measure outcomes. Current problems with clinical outcome measurement: relevance, heterogeneity in the way things are measured and feasibility. In a review of clinical trials, 39/49 outcomes were measured and reported in ≤50% of studies. ICHOM consortium has developed an agreed standardised set of outcomes that should be measured and reported as a minimum set of outcomes in trials, which is informed by a lived experience perspective. NINDS epilepsy Common Data Elements project as a standard-setting tool for epilepsy research. Built on by Murugupillai et al in 2018 looking at paediatric outcomes, and also in UK in CHOICE (Core Health Outcomes in Childhood Epilepsy) which looked at usual seizure outcomes, developmental outcomes, schooling and QOL. Difference in priorities of various stakeholders e.g. sleep-related outcomes more important for patients than health professionals. All studies basically using Delphi consensus process. Personalised outcomes do need to be considered beyond what is reached by consensus e.g. driving status, schooling, personal costs, mental health. www.comet-initiative.org/studies

3. **Talk 3: Are all epilepsies the same? Different measures for different epilepsies.**
   Patient perspectives for Angelman syndrome, CDKL5 mutations in terms of neurologic and non-neurologic symptoms that impact QOL and are major concerns for patients and families. Treatments which target the fundamental basis of a condition and aim to improve the entirety of the phenotype are not necessarily a cure i.e. disease-modifying treatments. Challenges for DMT-trials are different to "pure" epilepsy trials: smaller cohorts, longer durations needed for developmental outcomes, may require historical cohorts. Option of stepped wedge or randomisation start trial if not possible to do a fully-blinded RCT. Seizure frequency as primary outcome is problematic: many genetic epilepsy syndromes have a range of seizure types and frequency e.g. STXBP1 often has seizures in first year of life (89%) but achieve seizure remission yet go on to have poor developmental outcomes. Any measurement of DMT needs to take into account multiple outcome measures, but there are multiple tools already available e.g. Pediatric Sleep Questionnaire, Rett Gross Motor Scale. However, also lack of outcome measures specifically validated in DEEs – does every gene need a specific severity assessment though? CDKL5 clinical severity assessment (clinician and caregiver assessments differ) as example of genetic DEE that has international group looking at relevant outcome measures. Process of developing an outcome measure slide.

4. **Talk 4: Predicting outcome from epilepsy surgery.**
   Temporal lobe surgery has good outcomes in terms of seizure control but has also been shown to have good outcomes for the average patient in terms of school attendance and QOL. Personalised medicine though means that algorithms are generated from large data

sets then applied to specific individuals with a great deal of accuracy using supervised machine learning. But the main limiting factor (apart from problems inherent in machine learning and AI and relative inflexibility) is that it requires very large amounts of data and in certain populations there are large numbers of predictors and small numbers of patients affected. Currently studies on use of well-developed AI do not show superiority in the performance of AI in predicting seizure freedom versus the clinical team.

5. **Talk 5: Will IGAP help to achieve meaningful outcomes?**
   Global instruments like Advocate's Toolkit for making epilepsy a priority in Africa. Comprehensive overview of what specific actions are needed to implement the key recommendations of IGAP. In countries where epilepsy falls under mental health i.e. LMICs, 2.5% of total expenditure on epilepsy also was spent in those countries in 2021.

Reducing treatment gap and mitigating economic complications in paediatric epilepsy.

1. **Talk 1: Treatment gap in paediatric epilepsy.**
   Epilepsy incidence 4 times higher in LMICs versus HICs. Causes for the disproportionately higher incidence (and prevalence?) not clear. Patients without a defined aetiology more frequently found in low-middle income socioeconomic settings, even in countries like Scotland and New Zealand. Definition of treatment gap is difference between person living with epilepsy (PWE) with active epilepsy who were appropriately diagnosed but did or did not receive appropriate treatment. Proportionate inverse relationship between World Bank income category and treatment gap according to WHO 2010 report. Role of hidden bias due to ethnicity/culture/race between patients (likelihood to see healthcare) and health professionals (likelihood to provide broader range of diagnostic options and treatment). Also role of easier access to information via social media and internet which is not vetted and can impact treatment choices from the patient side. Role of traumatic brain injury, infections and perinatal HIE in low-resource settings. Role of health professional training, awareness of and access to treatment options, availability of surgical options for focal epilepsy in resource-poor settings. Absence of published research from most of Africa (Jo's 2021 paper Ann Neurol). As per reports by Reynolds et al and Siyoon et al, mere delivery of drugs to resource-poor countries may not necessarily translate to a reduction in the treatment gap or QOL.

2. **Talk 2: Structured interventions in a busy clinical setting.**
   Four levels of intervening a) systems-focused practice e.g. clinics, administrators etc b) public health policy e.g. guidelines on delivery and access to care c) community-focused practice e.g. community knowledge, behaviour and attitudes and d) Individual or family-focused practice. Structural interventions improve health by altering the structural content in which health is provided. Community-based prevalence studies show epilepsy 5 per 1000 people based on Kenyan data within some regions approx. 50 new cases of epilepsy per month based on complete data from 2022. Critical shortage of human resources to meet this need – need to increased workforce by 150% to meet this level of need. Structured interventions need to be sequential and brief and evidence-based. Decision to make regarding technology versus paper-based, with leveraging of technology-based options ideal. Focus on priority problems that are amenable to change (high yield). Criteria for evaluating interventions: rigour and relevance; efficiency and speed; collaboration and improved capacity. Role of education in reducing stigma but needing to include traditional health practitioners and

teachers in Kilifi. Example in early 2000s amongst various stakeholders in India to provide ASMs with 30% reduction in costs, patients receiving 70-95% of drugs prescribed and 80% of prescriptions being from EDL. Role of psychoeducation interventions delivered by clinicians improved adherence to ASM. Systematic assessments beyond epilepsy required using structured or semi-structured tools and strengthening information systems for online data capture. Additional benefit in Kilifi of reducing stigma amongst nurses and CHW with education and training for detection of neurological disorders in the community.

3. **Talk 3: Education and health literacy – building a training program for people with epilepsy and their families.**
   Reduced health literacy can cause parents to develop negative attitudes, impose unnecessary restrictions and make choices with further negatively impact on QOL. Health literacy is at the level of the individual and their ability to interrogate the information provided to them, but also at the level of the clinician/institution and their ability to communicate effectively important information about the condition. Multiple concerns of caregivers (affected child, siblings, risk of seizures, QOL) are aggravated by lack of health literacy. Health literacy challenge is knowing where and how to find accurate and relevant information especially because of easy access to internet. Online resource: www.clinictocommunity.ca with group for coordinated care for people with epilepsy. Stepped programme with baseline information including seizure type, first aid, school support etc then at each follow up newer topics are introduced and older ones revisited. Advocate's toolkit for reducing epilepsy stigma in Africa.

4. **Talk 4: Domesticating the IGAP's 90-80-70 cascade target for the epilepsy treatment gap in LMIC settings.**
   Lack of prevalence data in Africa on epilepsy so how do we even start measuring first target of IGAP i.e. 90% to know their diagnosis. How can the treatment gap better consider the social context in which epilepsy challenges arise, acquire meaning and are responded to? Lack of social response i.e. treatment gap ignores effective psychological interventions, stigma, poverty and impact of social and economic policy interventions in improving health. "Governments work is to domesticate – our work is to advocate". Implications include funders being keen on treatment gap but individual treatment focus will not have a population impact. Also need to look at the "care gap"= treatment gap +psychosocial gap +physical healthcare gap.

Neonatal seizures and epilepsy – from the past to the future.

1. **Talk 1: New ILAE classification of neonatal seizures.**
   Seizures common in neonatal period but usually symptomatic/provoked (85%) and HIE primary cause in most cases. No classification for neonatal seizures. NS limited to focal onset. Videos and case examples given of each major subtype of NS. Motor myoclonus typical for DEEs or metabolic disorders, but cannot be distinguished from benign myoclonus of infancy and need EEG. Motor (oral) automatisms can be seen as part of HIE picture because of hyper-excitability but most often are not seizures – again need EEG to correlate. Motor sequential seizures (moves from one motor subtype to another throughout the course of the seizure) possibly associated with metabolic or genetic causes (e.g. KCNQ2-related epilepsies or other channelopathies). Slide on validation of neonatal seizure classification. 10-15% of all neonatal seizures are the onset of an early infantile epileptic

syndrome. *EEG needs to be part of neonatal seizure classification. Some seizure types are indicative of certain aetiologies.*

2. **Talk 2: Neonatal EEG monitoring rationale and classification.**
   Clinical and EEG data do not predict seizure occurrence well, but models combining both may aid targeting. Most seizures on EEG do not have a clinical correlate in babies. Medications such as phenobarb can lead to uncoupling of clinical and EEG pictures. In studies from Riley and Alberta Hospitals with implementation of standardised EEG-based neonatal seizure protocol, good outcomes in terms of frequency and use of ASM (reduction) and reduced length of stay, also increased detection of NSE. Electrographic seizure burden associated with worse MRi injury and developmental outcomes – which comes first? Primary insult leading to seizures versus seizures being the insult leading to long-term poor neurodevelopmental outcomes? Seizure burden over prolonged period (>48 hours) associated with poor outcome versus favourable outcome in those whose ES terminated prior to that point. EEG forms an important part of the decision pathway for management of neonatal seizures (either cEEG or aEEG). Even in resource-intensive settings with access to cEEG for all at-risk neonates, 1/5 neonates without ES still received a ASM and 1/5 of those with ES on cEEG did not receive ASM. Sensitivity and specificity variable and highly dependent upon the skill level in interpretation. Problem with aEEG is the relatively brief duration of seizures versus the time needed to record the electrographic event with compressed (aEEG) data. In the setting of high seizure incidence/risk (e.g. HIE) and high experience, aEEG can significantly increase likelihood of detecting NS, but with decreasing levels of experience, utility of aEEG significantly decreases.

3. **Talk 3: Diagnosing neonatal seizures earlier and more efficiently.**
   HIE and stroke associated with worse neurodevelopmental outcomes compared even to ICH. Slide on EEG changes and semiology. Machine learning was as good as expert opinion in combining clinical and EEG data in detecting seizures. NS will emerge earlier depending on aetiology e.g. metabolic>severe HIE>moderate EEG. Real-time use in some centres of automated/ AI programmes to detect seizures has offered alternative especially for after-hours or times when neurologist/neonatologist not available to handle queries immediately.

4. **Talk 4: New definitions and guidelines for NSE.**
   Duration of EEG seizures in data is a potentially modifiable risk factor for epilepsy in childhood. Majority of neonatal seizures last 1-5mins, but high risk of adverse outcome after 10mins of seizure. New classification system uses 4 axes: a) semiology b) aetiology c) EEG correlates and d) age. Both seizure frequency and burden correlate with neurodevelopmental outcome. ASM reduces amplitude and propagation of NS and promotes electroclinical uncoupling, which can make seizure detection more difficult.

5. **Talk 5: New ILAE seizure treatment guidelines.**
   Phenobarbital superior to LEV as first-line ASM in achieving termination of seizures in neonates (80% vs 28% based on RCTs alone). Phenobarb should be first-line ASM irrespective of aetiology but can consider sodium channel blocker if channelopathy is a consideration. In neonate with cardiac disorders, LEV may be considered as second-line ASM in preference to phenytoin. Following resolution of acute provoked seizures, ASM should be stopped prior to discharge home. Slide on treatment algorithm for NS.

IEC2023: Monday 4 September 2023

Newly-diagnosed epilepsy: identification and intervention of neuropsychological sequelae

1. **Talk 1: Patient-centred perspectives.**
   Two community members (one PWE and one parent of PWE) discussed their experiences especially in terms of neuropsychological sequelae of epilepsy from diagnosis through therapy to current situation for them.

2. **Talk 2: Neuropsychological problems and underlying mechanisms in children with newly-diagnosed epilepsy.**
   If we start near the time of epilepsy diagnosis, medication use less (probably haven't worked through lots of ASM or on multiple pharmacotherapy), fewer seizures occurred, increased understanding of when and how cognitive development is impacted because you can more clearly delineate timeline of changes from early on in the process to current. Children who have seizures prior to age 2 appear to be at highest risk for cognitive delays. Almost 1/3 of children with no clear aetiology for their epilepsy have been found to have developmental/cognitive delay. In German study, relative risk for cognitive impairment was 1.7 even prior to epilepsy compared to general population, and majority of children had mild or unspecified cognitive impairment. In American study, greater difficulties with attention/executive function in absence and focal onset group and memory difficulties in generalised epilepsy group found; however, in Jackson et al 2013, cognitive abnormalities did not differentiate between epilepsy syndromes. Majority of studies have found associated neuroimaging abnormalities among children with epilepsy and cognitive fallout. Scottish study: social disadvantage was not associated with genetic risk or increased structural causes for epilepsy among children with a known aetiology, whereas there was a significant association for children with unknown aetiology for epilepsy. Summary:
   a) Seizures prior to age 2 increase the risk for cognitive impairments
   b) There is a substantial proportion of children who have seizure-onset between ages 2-5 that are still at risk for cognitive impairments. This group is understudied.
   c) Cognitive impairments can occur before seizure onset but in younger children, milder cognitive impairments may be identified later at school.
   d) Cognitive impairments may not be specifically associated with epilepsy syndromes
   e) There appear to be underlying changes in brain structure, including GM and WM changes associated with cognition.
   f) There may be modifiable risk factors associated with social deprivation and sleep that can be addressed to improve cognitive outcomes
   g) Early cognitive interventions may be beneficial

3. **Talk 3: Neuropsychological problems and underlying mechanisms in adults with newly-diagnosed epilepsy.**
   Not immediately relevant to paediatric neurology.

4. **Talk 4: Neuropsychological interventions in newly-diagnosed epilepsy – a review of available evidence.**
   Co-morbidities are evident before seizure-onset but we do not always know the natural history or who is at more risk compared to other groups of PWE. Evidence that patients often attribute the neuropsychological deficits they experience directly to the mechanism of ASM. Relatively few longitudinal studies charting the cognitive course of epilepsy. Cochrane

Epilepsy Group found only 2 observational studies that looked at neuropsychological interventions for adults LWE, so could not perform meta-analysis and no RCTs looking at ameliorating cognitive impairment among PWE.

5. **Talk 5: Management of newly-diagnosed epilepsy in both resource-plentiful and resource-limited settings.**
   ILAE recommendations endorse routine screening for cognition, mood and behaviour in new-onset epilepsy. Routine screening provides an efficient and relatively inexpensive method for identifying people who require more detailed neuropsychological assessment. It also functions as a minimal baseline to measure the cognitive course of a PWE. Modes of care are shaped by funding source, recognition of need for neuropsychology, relevant/available human resources and clinical-research nexus. Melbourne model presented – well out the reach of SA. SA context presented by Aimee Dollman. 100-200 neurologists for 59 million people based on 2020 survey. Private medical insurance will often cover for medical treatment but not neuropsych assessments. Private neuropsychologists often do not have specialised or extensive experience with PWE, especially more complex cases. No funded neuropsychologist post in public sector. Indian context also presented.

ILAE syndrome classification as roadmap for epilepsy-associated comorbidities

1. **Talk 1: Autism Spectrum Disorder in Developmental and Epileptic Encephalopathies – under- or overrated?**
   Prevalence of ASD higher among those with epilepsy syndromes compared to other epilepsy types. Prevalence around 1.5-3% but can be as high as 40% in syndromes. Prevalence of ASD 22-46% using ASD-specific instruments for children with Dravet versus very low prevalence (apparently) among those with LGS. Widening of what falls under ASD can also impact on reported prevalence over time. Suggested that ASD is actually underdiagnosed in children with DS, with issues around instruments typically used to measure and "gold standard" still considered clinical judgement. Data on whether ASD symptoms can be reduced in DS not yet available even with successful management of seizures e.g. with fenfluramine. >50% of children with DS scored as at risk for ASD using SCQ, ADOS and DBC-ASA subscale. Those children then underwent assessment with DSM-V criteria and 60% were met criteria for ASD. Phenotype of ASD may not follow usual trajectory among children with DEEs. Need for further work on the evolving phenotype and natural history of ASD among the DEEs.

2. **Talk 2: Delineating behavioural and cognitive phenotypes in JME.**
   JME has polygenic inheritance. Photosensitivity (90%), chronodependency (worse in morning) and polypharmacy well-described in JME. Multiple JME subsyndromes as well, with prognosis often worse in these. Paper: atypical EEG abnormalities in genetic generalised epilepsies. 75% achieve seizure control, 15% refractory and 10% pseudo-refractory (related to misdiagnosis). Executvie/attentional deficits present in 63% of people with JME in some populations, and usually mild-moderate in severity. Risky decision-making and novelty-seeking behaviour may be particularly relevant in those with poorly controlled seizures. Impulsive traits also notable in JME. 20-30% have psychiatric disorders e.g. personality disorders, mood disorders but again usually mild rather than automatically severe. Memory problems not usual in JME but can occur, and usually in the context of difficult to control seizures.

3. **Talk 3: Epilepsy syndromes with onset at a variable age – red flags for behavioural and psychiatric comorbidities in focal epilepsies.** Focus on adults in this lecture. Many brain regions involved in epilepsy e.g. TLE where frontal limbic networks are involved, are also involved in mood disorders such as depression. Different mechanisms result in similar outcomes so far in limited research e.g. hyper- and hypoconnectivity both involved in depression.

4. **Talk 4: Using the ILAE syndrome classification as a roadmap to think about comorbidities screening and diagnosis**
   Using TSC-associated neuropsychiatric disorders as example of where DEE can help identify specific co-morbidities to screen for in particular patient groups. Important to distinguish regression from plateau. LGS is an example of where regression versus plateau can be difficult to distinguish especially when you need to act urgently with controlling the seizures. Children with spasms start with developmental regression but then it may be difficult to tell when the degree of recovery is sufficient or a plateau. Children with EE-SWAS have normal development until onset of the EE and then experience cognitive regression, behaviour changes, motor regression and autistic features as part of the syndrome. Encompasses previous separate syndromes of encephalopathy with CSWS, Atypical Benign Focal Epilepsy of Childhood and Laundau-Kleffner. They should be expected to regain normal cognitive function once the EE is controlled. In situations where there is no DEE, e.g. SeLECTS, you can warn caregivers to watch for regression which is NOT expected, in case the epilepsy has been mislabelled and is an evolving syndrome. Genetic generalised epilepsies can be divided into idiopathic generalised epilepsies (e.g. CAE, JAE, JME, GTCA) and EE (epilepsy with myoclonic-atonic seizures – EMAS), DEE (epilepsy with eyelid myoclonia – EEM; epilepsy with myoclonic absences – EMA) and DE (myoclonic epilepsy in infancy – MEI). IGEs have executive function disorders rather than pure ID. Higher incidence of ADHD in SeLECTS and CAE (inattentive subtype). Concerns around methylphenidate worsening seizure frequency are largely unsupported. May occur in up to 18% but is usually a mild and transitory effect and leads to discontinuation of the medication in <5%.

Hypothalamic Hamartoma – evolving understanding of evolution and treatment of an epileptic syndrome

1. **Talk 1: Genetics and clinical work-up for HH – what do we need?**
   Developmental lesion and rare – 1 in 200 000 children. Two broad anatomico-clinical forms: Intra-hypothalamic associated with refractory epilepsy, neuropsychiatric morbidity, and para-hypothalamic associated with precocious puberty but usually no seizures. Epilepsy syndrome associated with HH is gelastic seizures, typically from neonatal period. Other seizure types appear from infancy including focal seizures with LOA and atypical absence/tonic/atonic/GTC seizures, representing a EE or LGS-spectrum, especially if associated with regression. Serious associated behavioural co-morbidities including rage attacks, sudden and explosive, not well-understood. Seizures are usually drug-refractory, but HH can also have a milder clinical impact with gelastic seizures only manifesting as a "pressure to laugh". Almost always sporadic, but syndromic form is Pallister-Hall syndrome where HH associated with polydactyly, epiglottic/laryngeal clefts, GU anomalies, hypopituitarism (rare) and gelastic epilepsy with cognitive/behavioural changes (uncommon) i.e. epilepsy not prominent; so usually it is the non-syndromic form that presents to

neurologists because of the epilepsy. Non-syndromic HH ~15% post-zygotic mosaic GLI3 mutation if resected tissue specimens tested.

2. **Talk 2: Cognitive and behavioural development in HH – what do we know?**
   Cognitive phenotype very diverse: 42-47% with GDD/ID; 33% speech and language impairment; 52% impaired executive function. >50% psychopathological findings including ODD, ADHD and conduct disorders. 20% may have ASD and mood disorders. Course can be progressive, with cognitive and behavioural deterioration over time. Cohort of 111 children in Freiburg 1999-2023: 47% had GDD/ID with epilepsy onset (earlier in those with GDD) being the biggest difference between those with and without cognitive fallout. Majority of these children have normal development prior to seizure onset but ~10% did have preceding developmental delay. Those with developmental delay prior to seizure onset had larger hamartomas, more interictal epileptic discharges and more often pathological EEG background activity. Central precocious puberty not significantly associated with GDD. Higher seizure burden (frequency rather than type) is associated with cognitive fallout – usually requires more ASM as well with its own effects. Positive effect of seizure cessation post-surgery with 45% of post-surgical cohort showing improved behaviour as well. Surface EEG more likely to show bilateral discharges in frontal and temporal regions with earlier propagation among children with GDD. Pathological background EEG activity was found to be most significantly associated with GDD of all the factors examined.

3. **Talk 3: To treat or not to treat: the role of gelastic and other seizure types**
   Gelastic seizures are the hallmark of HH and often the first symptom that is seen. Focal seizures often have a frontal or temporal lobe profile (see lecture above). Gelastic ->focal aware seizures -> focal impaired awareness seizures with secondarily generalised seizures - > epileptic encephalopathy with behavioural disorders and cognitive regression. As clinical picture evolves from focal disease to focal advanced disease to extensive disease, EEG also involves from focal epileptogenic foci to disseminated interictal pathology to widespread ictal EEG patterns. Hidden seizure burden especially nocturnal period and in early childhood where focal seizures are predominant – may manifest only as severely disturbed sleep. Gelastic seizures come predominantly from the HH but other seizure types originate from other parts of the brain, suggesting that epileptogenic networks develop over time ?is earlier treatment therefore better. Alternatively, is it a multifocal disease with other areas being particularly prone to develop epileptogenic foci given the underlying genetic mosaicism. No effect on gelastic seizures of ASM – needs surgical management. Most often tried are sodium channel blockers for other seizure types.

4. **Talk 4: New treatments for unilaterally and bilaterally attached hamartomas**
   Neurosurgical discussion on various techniques and outcomes for surgery.

IEC2023: Tuesday, 5 September 2023

Immunity, inflammation and epilepsy

1. **Talk 1. Immunology underlying autoimmune epilepsies.**
   Overview of immune mechanisms related to encephalitis. Example of Rasmussen's. Staging of Rasmussen based on histopathology. CD8-mediated killing in early GAD encephalitis. Looked at various types of immune mechanisms and histopathology across a range of immune-mediated encephalitides. Essentially, varying levels of T-cell infiltration and complement deposition.

2. **Talk 2. Epileptogenic mechanisms of human autoantibodies.**
   GABA(A) receptor encephalitis rare but severe autoimmune encephalitis with high mortality. GABA(A) Abs directly and immediately affect GABA(A) receptor inhibition. LGI1 encephalitis is a limbic encephalitis. LGI1 neuronal secreted protein that links presynaptic potassium channels with postsynaptic AMPA receptors – antibodies lead to inhibition of protein-protein interaction.

3. **Talk 3. Management of patients with suspected autoimmune epilepsy.**
   Helps to distinguish autoimmune encephalitis from autoimmune epilepsy. LGI1>NMDAR>onconeuroal>CASPR2>GABA-R in terms of frequency of antibody positivity in first acute seizures (not epilepsy).

4. **Talk 4. AE in paediatric patients.**
   Among children, MOG>AQP4 and NMDA>LGI1. GAD very rare in children.

Complex and rare epilepsies: the past, present and future

1. **Talk 1. Parent perspective on complex epilepsy.**

2. **Talk 2. DEE: the need for an aetiology-driven approach.** Recap of 2022 ILAE classification of epilepsy syndromes. >925 monogenic epilepsy genes and >825 genes are related to DEEs with 50% solved. Finding the cause ends the diagnostic odyssey and informs co-morbidities, prognosis and likelihood of drug resistance and to optimise treatment and perform genetic counselling. Examples of specific genetic and metabolic aetiology DEEs given.

3. **Talk 3. From catastrophic epilepsies to DEE – what is in a name?** EIDEE is usually drug-resistant, may evolve to IESS, nearly all have moderate to profound ID and concomitant other neuro disorders (e.g. movement disorders), high mortality (45%) with most deaths early in life and due to sequelae of impairments eg. aspiration pneumonia. IESS has broad range of aetiologies, onset between 1-24 months; spasms usually stop before 3 years, 18% evlev to LGS, 36% seizure-free and 55% have DRE; 1/3 die by adulthood with significant impairment amongst survivors. Evidence that initiation of vigabatrin with ES only in IESS lead to better outcomes. Chiron et al DMCN 2023 on earlier use of initiating STP <2yrs of age reduced prolonged TCS and SE. Some evidence that better seizure control results in better non-seizure outcomes (post-hoc analysis in fenfluramine OLE study). ASO therapy being used in trials in DS 2-18yrs of age, resulted in dose-dependent seizure reduction.

4. **Talk 4. The unmet needs in the transition to adult care in DEEs.** Many monogenic DEEs survive into adulthood and have complex care needs. Seizure semiology and timing may change with age (e.g. DS) as so trigger factors. Some seizure therapies are less used in adults (vigabatrin, fenfluramine and ketogenic diet). Impact of ASM differs among age groups, and so do side-effects. Reproductive health and autonomy become important issues in adolescence and specific services oriented to this are helpful as part of transition.

5. **Talk 5. Management of DEE in low-resource settings.** No community-based data in Africa. Rely on hospital-based data. 50.7% of children presenting with IESS in Tanzania had a perinatal insult. 0.003 child neurologists per 100 000 children in Africa (WHO data). Treatment gap 60% in urban areas and up to 90% in rural areas – main reasons are cost and personal belief (spiritual rather than biomedical causes). Traditional healers 5 per 1000 people (higher than health professionals). Up to 80% of people will consult TH first before doctors – mean duration 39 months between TH and health facilities. Parent-led groups in Africa instrumental in addressing stigma, raising awareness and educating communities around epilepsy (Tanzania has some very good examples).

6. **Talk 6. Epilepsy surgery in DEEs.** Longer latency to surgery resulted in reduced positive outcomes both for seizure freedom and DQ. Studies of children with LGS showed excellent outcomes with CC and resection where indicated. VNS and CC both results in seizure reduction in children with LGS. Stevelink et al 2018 showed good results for epilepsy surgery in children with mutations in MTOR pathways and visible lesions on MRI, but poor results for mutations involved in channel function and synaptic transmission. Important considerations for surgery: early referral and evaluation; thorough pre-surgical evaluation and proper counselling.

Identifying and managing neurobehavioural comorbidities in children with epilepsy – can we bridge the gap?

This session comprised 4 different speakers, including Prof K Donald HOD of Developmental Paediatrics at UCT. The first presentation was by the parent of a British child with severe behavioural comorbidities who had struggled to receive proper attention and assistance from the National Health Service in England despite the child having several recognised co-morbid conditions apart from her epilepsy. It was a heart-breaking story and one all too familiar to families here in South Africa. The second presentation was on the range and frequency of co-morbidities among children with epilepsy (e.g. ASD in DS) but did not cover new ground to some of the sessions above. There was good evidence presented of the benefit of having dedicated screening tools for specific co-morbidities for children with particular epilepsy syndromes that clinicians can use at review appointments. The value of having a mental health service integrated within the neurology service was also emphasised, but lack of cohesive services is a widespread problem across every income setting. Prof Donald then spoke about this disproportionate disease burden in LMICs, the difficulties in disentangling co-morbid conditions from the underlying epilepsy (e.g. attention problems), the role of stigma and the impact on schooling. She gave examples from the South African context of collaboration and capacitation of professionals to perform multiple roles in order to meet the needs of these children. The suggested flow was 1. To have a “champion” in neurology and psychology, 2. To normalise having mental health conversations in clinics, 3. To de-stigmatise psychiatric services and 4. To track referrals and follow-ups. Additional considerations include early detection with scalable tools, care pathways, access issues and intergenerational considerations such as prenatal exposures. The final talk was around options for treating neuropsychiatric difficulties in children with epilepsy and delivered by a

psychiatrist. It gave a good overview of pharmacological and non-pharmacological options and emphasised the importance of putting together the child's entire picture and targeting medication choices across these needs e.g. a child struggling with sleep deprivation and epilepsy versus a child who struggles with attention at school and epilepsy. Also important to be aware of mood disorders and how ASM can exacerbate those. Choice of ASM should also consider any needs around mood.

Conclusion

I am very grateful to the Department of Paediatric Neurology for nominating and supporting my attendance at the ILAE leadership course and the IEC2023. I benefitted greatly from both events and will hopefully carry these skills and knowledge through to my work here in the department and beyond. It was also a pleasure to get to know several key colleagues in paediatric neurology from around South Africa and to strengthen those ties. Despite very little time outside the formal programme to explore, I was able to fit in a bit of tourism in Dublin itself and enjoyed those moments as well. It was a thoroughly successful and enriching experience and I hope at least some of the vast expertise I was exposed to has come through in this report.