International League Against Epilepsy (ILAE) 15th European Epilepsy Congress (EEC), 7–11 September 2024, Rome, Italy

A CONGRESS HIGHLIGHTS REPORT ON SELECTED SYMPOSIA PRESENTATIONS

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Saturday 7th September 2024

NEUROBIOLOGY SYMPOSIUM: INTEGRATING GENOMICS, NEUROPHYSIOLOGY AND PRECISION MEDICINE

Chairs: David Henshall, Ireland; Aristea Galanopoulou, US

The future of ASM use: Integrating genomics, neurophysiology and precision medicine

Raman Sankar (US)

Epileptic seizures occur due to an imbalance between excitation (e.g., increased sodium channel function, increased excitatory synapse function) and inhibition (e.g., decreased potassium channel function, decreased inhibitory synapse function).[1] Sodium channels, encoded by *SCN1A*, *SCN2A* and *SCN8A* genes, with corresponding $Na_V1.1$, $Na_V1.2$ and $Na_V1.6$ channels, contribute differently to excitability, depending on cell type and location of expression.[2] While depolarization involves sodium channel function, repolarization involves potassium channels (coded by *KCNA* genes).[2,3]

In epilepsy, $Na_V1.6$ and $Na_V1.1$ are key, with gain- or loss-of-function (LoF) mutations in the coding genes resulting in the disease.[4-6] Based on this, a promising therapeutic strategy for epilepsy could be selective targeting of $Na_V1.6$ to block persistent depolarization shift while sparing $Na_V1.1$, which can preserve inhibitory function and prevent exacerbation in conditions such as Dravet syndrome (caused by a LoF in *SCN1A*).

Despite advances in gene therapy and antisense oligonucleotide (ASO) therapy modalities, small molecule therapeutics remain the major option for most patients with epilepsy. Cenobamate selectively inhibits persistent sodium currents without affecting transient currents by selectively targeting $NA_V1.6$.[7] Successful treatment with cenobamate of patients with Dravet syndrome was demonstrated in a multicenter study.[8] Research has also been focused on developing compounds that are isoform-selective $Na_V1.6$ inhibitors, such as CNS-penetrant aryl sulfonamides, which showed activity in the mouse models, with some already on clinical trials.[9] For example, NBI-921352 demonstrated inhibition activity in firing in pyramidal neurons but sparing fast-spiking interneurons.[10] While carbamazepine markedly reduced firing in fast-spiking cortical interneurons, treatment with NBI-921352 resulted in slightly increased firing frequency.

Other emerging drugs include a new class of small molecule Na_V-targeting compounds XPC-7224 and XPC-5462, which showed considerably increased selectivity for $Na_V1.6$ and/or $Na_V1.2$ channels, and a >100-fold molecular selectivity against $Na_V1.1$ channels.[11] Another approach is to activate GABAergic interneuron chemically.[12] The small molecule AA43279 increased the firing activity of parvalbumin-expressing, fast-spiking GABAergic interneurons, in rat hippocampal brain slices. Furthermore, persistent sodium current modulators such as GS967 (PRAX330)

may be an effective precision targeting strategy for *SCN8A*-related encephalopathy and other functionally similar channelopathies.[13,14] Research also shows that cannabidiol preferentially inhibits resurgent currents over transient currents;[15,16] however, these results are yet to be confirmed.[17]

How are functional studies guiding our choice of antiseizure medication for GABA-related disorders?

Rikke Møller (Denmark)

The GABA-A receptor plays a crucial role in ion channel inhibition in the mammalian brain.[18] It is a pentameric structure assembled by five subunits (mainly one gamma, two alpha, and two beta subunits), with 19 different subunits encoded by 19 genes.

Genetic variants in the GABA-A receptor are associated with a spectrum of neurological conditions, including epilepsy, intellectual disability, motor impairment, language impairment, movement disorders, autism spectrum disorder, ADHD and schizophrenia. A genetic variant in the GABA-A receptor can alter the sensitivity to GABA, affect the assembly of the receptor and trafficking of the receptor to the cell surface, and impact GABA binding, gating and desensitization. For example, genetic variants in *GABRB2* (encoding the ß2 subunit of GABA-A) can lead to both gain-of-function (GoF) and loss-of-function (LoF), which are correlated with distinct disease manifestations.[19] Similar data were reported for other *GABA* receptor genes, all showing a phenotypic difference between LoF and GoF mutations.[20-25]

Based on these data, patients can be grouped according to the functional effect of their variant, which may impact treatment choices. A recently conducted caregiver survey via the patient advocacy groups revealed that patients with LoF variants respond well to clobazam, clonazepam, stiripentol and valproic acid, while the most effective drugs in the GoF group are cannabidiol, phenytoin, carbamazepine, phenobarbital and valproic acid.[26] Furthermore, the LoF patients often experience worsening when treated with sodium channel blockers, while GABAergic drugs cause worsening in the GoF cases.

Data further show that specific variants in the *GABRB3* gene are linked to vigabatrin hypersensitivity in a subset of patients associated with hypotonia, sedation and respiratory suppression.[27] In addition, preclinical research and case reports showed that vinpocetine has potential efficacy in treating patients with select GABRB3 mutations.[28-30]

Sunday 8th September 2024

LATE ONSET EPILEPSY – A PUBLIC HEALTH IMPERATIVE

Chairs: Eugen Trinka (Austria); Hermann Stefan (Germany)

Pathogenesis of epilepsy in the elderly – The "Bermuda Triangle" between dementia, depression and sleep disorder

Arjune Sen (UK)

Sleep plays an important role in epilepsy and cognitive health.[31] Non-REM sleep helps establish synaptic homeostasis, reshape cortical networks and can activate interictal epileptiform discharges (IEDs), which may disrupt hippocampal and thalamic coupling, and frontal networks. High-quality data on sleep-related memory consolidation in epilepsy are limited, with some studies demonstrating the adverse impact of sleep-related epileptic activity and impairments in children with epilepsy.[32] In patients with temporal lobe epilepsy, data show reduced sleep efficiency, frequent shifts between sleep stages and sleep apnea.[33]

In Alzheimer's disease (AD), which is frequently associated with seizures (especially the familial form34), early symptoms include poor sleep quality and decreased REM sleep, which contributes significantly to tau and amyloid deposition associated with neuronal hyperexcitability. By using sleep EEG, studies have shown silent hippocampal seizures and epileptiform spikes during sleep (predominantly non-REM sleep) in AD patients with epilepsy,[35-37] while others have suggested no change between AD versus mild cognitive

impairment versus healthy controls.[38] Increased gamma connectivity has been recently noted in stage 2 sleep in those with AD.

The association between sleep, IEDs and memory has been shown in a recent study, which indicated that epileptic activity detected on foramen ovale electrodes during sleep is associated with tau pathology in AD.[39]

Modulation of brain hyperexcitability is a potential therapeutic approach for AD. Antiseizure medications have shown promise in suppressing hyperexcitability and restoring balance within cortical networks in AD patients.[40]

The interaction between epilepsy, sleep disturbances and AD is dynamic and changes over time, for example, increasing tau load, and changes in fMRI and lymphatic function.[41] To understand how these factors evolve as AD progresses, longitudinal studies are needed.

It was also recognized that many vascular dementia risk factors contribute substantially to late-onset epilepsy and that controlling these factors in midlife may improve health outcomes later in life.[42] Data showed that people with epilepsy experienced accelerated cognition decline versus people with stroke, particularly those with high cardiovascular risk.[43]

Mood disorders are also common in epilepsy, with around one-third of patients with epilepsy experiencing clinical depression and 10% having anxiety. Furthermore, sleep in depression is characterized by alterations in sleep continuity and 75% of people with depression report insomnia.[44,45] Neurodevelopmental disorders such as ADHD and autism are overrepresented in epilepsy and are often associated with sleep difficulties.

Obstructive sleep apnea (OSA) and insomnia are other relevant comorbidities in epilepsy.[46,47] OSA potentially causes disturbances in the cortical network through hypoxia, which may increase hyperexcitability. Treating OSA can be beneficial in improving sleep quality and daytime alertness in patients with epilepsy.

Diagnostic challenges in the new onset epilepsy in the elderly

Taoufik Alsaadi (UAE)

Epilepsy in older patients is often defined for those above 60 or 65,[48] with incidence increasing sharply, especially among those over 75. Older people have 2–3 times higher seizure incidence compared with younger populations.[49-54] Data also showed an incremental increase in the incidence of epilepsy in patients above 85, with a higher prevalence in black patients, regardless of age or gender.[55] The overall mortality risk for older patients is 2–3 times of the general older population.

Seizures in older patients are easier to control,[56] but they are more prone to treatment side effects and increased comorbidity burden compared with younger patients. Older patients may also experience prolonged postictal states (up to a week in a proportion of patients)[57] and increased risk of stroke, dementia, serious injuries and fractures due to falls, which are frequently caused by cognitive and visual impairment and balance issues.[58]

Diagnosing epilepsy in older adults can be challenging, with delays of up to two years (in 25% of the population) due to atypical presentations, complexity of symptoms, concomitant medications and comorbidities. In terms of clinical manifestations in older patients, aura and automatism are less frequent, while postictal confusion can be prolonged.[59] There is also a lower incidence of psychic exponential symptoms.[60] Focal impaired awareness is the most common seizure type (40%), and generalized tonic-clonic seizures occur less often (<30% vs 65% in younger patients).[60,61] A subset of older patients may present with status epilepticus (25–30%).

EEG abnormalities are also challenging, as normal variants are often misinterpreted as epileptiform activity.[62] Routine EEGs may appear normal in 25–35% of older patients with new-onset or pre-existing epilepsy.

Several etiological factors have been identified, predominantly stroke, dementia, Alzheimer's disease and neoplasms.[63-67] Brain tumors are the second most common

cause of epilepsy in older people, with seizures as presenting symptoms in 20–40% of patients with brain tumor.

High rates of comorbidities complicate the management of epilepsy, such as dyslipidemia (80%), hypertension (65.8%), stroke (50.7%) and cardiac risk factors (48.1%), as well as neurological and psychiatric conditions (depression, psychosis and schizophrenia).[66,68,69]

Antiseizure medicines for epilepsy in the elderly – between Scylla and Charybdis

Eugen Trinka (Austria)

Acute symptomatic seizures in older patients are associated with higher early mortality rates but a lower risk of subsequent unprovoked seizures, although a high relapse rate can complicate management.[70-72] There are several complicating factors in older patients, including increased sensitivity to antiseizure medication (ASM), altered pharmacokinetic and pharmacodynamics, comorbidities (cirrhosis, renal insufficiency, dementia, depression) and polypharmacy.[65,73]

Cognitive-behavioral screening of 257 older patients with new-onset epilepsy showed a relatively high quality of life (QoL), although 60% of patients had cognitive impairment at their first seizure, with neurological status and body mass index as significant risk factors.[74] A latent class analysis further identified associations between newly-onset epilepsy and comorbidities, with a cluster mainly consisting of patients with mixed seizure types, higher age and multiple somatic comorbidities (stroke, cardiovascular diseases), who were at a higher risk of affective disorders.[75]

Only a few randomized control trials assessed treatment for seizures in older patients. This includes a study that showed no difference in seizure control between lamotrigine and carbamazepine immediate-release (IR), although the withdrawal rate was doubled with carbamazepine.[76] In another study, carbamazepine IR was also associated with significantly worse outcomes versus both gabapentin and lamotrigine in new-onset geriatric epilepsy.[66] However, while carbamazepine sustained-release (SR) achieved comparable activity to lamotrigine,[77] the STEP-ONE study showed that both levetiracetam and lamotrigine had improved clinical activity compared with carbamazepine SR,[78] which was supported by the findings from the KOMET study.[79]

A retrospective review comparing ten antiepileptic drugs in older adults further found that lamotrigine had the highest retention rate (79%).[80] While a systematic review and a network meta-analysis showed no difference in seizure freedom between levetiracetam and lamotrigine, the rate of adverse events was higher with levetiracetam,[81] probably because of decreased clearance of levetiracetam after 50.[82]

Regarding safety, chronic effects of enzyme induction were reported with older ASMs,[83] mainly due to drug-drug interactions, gonadal steroids, vitamin D levels and osteoporosis, and lipid profile and cardiovascular risk (statins).[84-86] However, a more recent study showed that osteoporosis risk in epilepsy is independent of the type of drug used (enzyme-inducing or non-enzyme-inducing).[87] This aspect is important because of the increased risk of falls in the older population, which is associated with ASMs and is higher with all CNS-active drugs.[58,88-90]

Another challenge is the interaction between non-vitamin K antagonists and ASMs.[91-96] According to the European Atrial Fibrillation Society guidelines, only a few drugs can be used in epileptic patients receiving non-vitamin K antagonists (brivaracetam, lacosamide, lamotrigine), but these are not indicated for older adults. The ILAE guidelines recommend gabapentin and lamotrigine, but levetiracetam and lacosamide can also be considered.[97]

Can we predict and prevent epilepsy in the elderly?

Simona Lattanzi (Italy)

The most frequent cause of epilepsy in older patients is stroke (ischemic, 37%; hemorrhagic, 12%).[69] The SeLECT score is commonly used to predict epilepsy risk after ischemic stroke and includes factors such as stroke severity at baseline and the onset, etiology of stroke, acute symptomatic seizures, and cortical and middle cerebral artery territory involvement.[98] The SeLECT 2.0 had comparable optimism-corrected discrimination to the original model (0.77), but it has improved accuracy due to capturing very high-risk

cases. A modified SeLECT 2.0 score was recently proposed, as replacing baseline with posttreatment stroke severity may improve predicting post-stroke epilepsy (PSE).[99]

For predicting epilepsy after a hemorrhagic stroke, the most commonly used CAVE score is based on four variables (cortical involvement, the age <65 years, the volume of the hematoma and the occurrence of early seizures) and stratifies patients in low, medium and high-risk groups.[100]

A recent study showed that futile recanalization after endovascular treatment is associated with an increased risk of PSE due to occlusion of large vessels of the anterior circulation.[101] Data obtained with continuous EEG monitoring within seven days of stroke suggest that acute epileptiform abnormalities increase PSE risk by 12-fold.[102]

A study on focal epilepsy showed that the response to antiseizure medication (ASM) is etiology-specific and that ischemic stroke-related focal epilepsy had an improved rate of seizure freedom, with a better prognosis achieved with the lowest ASM load.[103]

Outcomes in patients with epilepsy are generally positive, but drug resistance may occur in 13–23% of PSE patients.[104-106] The latency period between stroke and the first unprovoked seizure has been recognized as a predictor of drug resistance in PSE.[107] A nomogram was developed to predict the risk of drug resistance in PSE, incorporating five variables: latency of PSE, status epilepticus at epilepsy onset, severe stroke, intracerebral hemorrhage and age at stroke onset.[108]

Preventing PSE mainly involves reducing the risk of stroke, which is associated with vascular risk factors such as hypertension and dyslipidemia, among others. While there are many interventions for this, targeting epileptogenesis after stroke remains challenging.[109] Preclinical models on drugs with epileptogenic effects in animals indicate that modulating multiple pathways simultaneously or sequentially may be more effective than a single-bullet strategy.[110] Another challenge is to define timing, as different mechanisms are active at the different stages during the latency, with altered gene expression progressing in waves (when to start and when to stop the treatment).[111]

Several clinical trials (with different designs, and treatment timing and duration) on ASMs, such as valproic acid, levetiracetam and diazepam, showed no clinical benefits in patients after stroke.[112] Ongoing studies on eslicarbazepine acetate, perampanel and perampanel-levetiracetam showed some early signals (particularly with eslicarbazepine acetate). Finally, post-stroke statin use may reduce the risk of early-onset seizure and PSE.[113]

MALUM QUO COMMUNIUS EO PEIUS: COGNITIVE PROBLEMS IN EPILEPSY

Chairs: Matthew Walker, UK; Nicola Specchio, Italy

Cognitive decline in the developmental and epileptic encephalopathies

J Helen Cross (UK)

Professor Helen Cross delivered a presentation on the cognitive decline observed in developmental and epileptic encephalopathies (DEEs), highlighting both conceptual frameworks and treatment approaches. The term epileptic encephalopathy was first introduced by Gastaut et al., referring to cases where epileptic activity directly hinders neurodevelopmental progress.[114] The Zuberi et al. paper further expanded on this, categorising DEEs as disorders in which developmental impairment arises from both underlying etiological factors and epileptic activity.[115]

Key distinctions were made between types of encephalopathies:

- Epileptic encephalopathy
- Developmental and epileptic encephalopathy
- Developmental encephalopathy with epilepsy

Emphasis was made that cognitive decline might appear as a stagnation or plateau, particularly when compared to peers. Standard IQ assessments often fail to capture changes in more severely affected individuals due to floor effects, which can obscure cognitive shifts.

Key Factors Contributing to Cognitive Decline:

Both underlying genetic causes and epileptic activity play significant roles in cognitive impairment. There is a strong overlap between genes linked to intellectual disabilities and those associated with DEEs. Acute cognitive deterioration can be triggered by non-convulsive status epilepticus, which may be subtle but critical to identify early.[116]

Treatment Insights:

Early interventions, particularly in infantile epileptic spasm syndrome, show the potential to improve cognitive outcomes by reducing EEG abnormalities.[117] Preventative strategies, such as those observed in studies on tuberous sclerosis (EpiPestop and PREVENT), have had mixed results. While preventative treatment helps with seizure management, there was no notable improvement in neurodevelopmental outcomes at two years. Following successful epilepsy surgery, medication withdrawal may improve cognitive outcomes, signalling the potential benefit of optimising treatment protocols post-surgery.[118]

Case Study – Dravet Syndrome:

Dravet Syndrome, once considered an archetypal epileptic encephalopathy, is now categorised as a developmental and epileptic encephalopathy. Patients with Dravet Syndrome are particularly prone to acute cognitive decline during status epilepticus episodes, some of which are accompanied by sudden cerebral edema.[119]

The presentation underscored the complexity of DEEs and the need for early, individualised interventions aimed at balancing developmental and epileptic treatment to manage both cognitive decline and seizures.

Epilepsy and cognitive decline: two sides of the same coin?

Terence O'Brien (Australia)

Professor Terence O'Brien's talk focused on the complex relationship between epilepsy and cognitive decline, emphasising the interconnected nature of seizures, cognitive function, and mood disorders. His presentation explored both the causes of cognitive issues in epilepsy and the potential links between epilepsy and neurodegenerative diseases like Alzheimer's. Cognitive dysfunction is extremely common in people with epilepsy, with up to 50% of newly diagnosed patients showing evidence of cognitive impairment. Cognitive function, along with mood and seizure control, significantly determines the QoL for epilepsy patients. Seizures, mood disorders, and cognitive dysfunction are part of the same epileptic substrate, suggesting that they are closely interlinked and influenced by similar mechanisms.[120–122]

Causes of Cognitive Disorders in Epilepsy:

• Cognitive impairment in epilepsy arises from various factors, including:

• Underlying brain conditions that cause epilepsy.

• Effects of anti-seizure medications.

• Comorbid mood disorders.

• The neurogenic effects of repeated seizures.

• Epilepsy as a result of neurodegenerative diseases such as Alzheimer's.

• Epilepsy possibly predisposing patients to neurodegenerative conditions.

Epilepsy and Neurodegenerative Diseases:

The incidence of epilepsy is highest among individuals over the age of 65, paralleling the rise in neurodegenerative diseases such as Alzheimer's. Alzheimer's patients are 6–10 times more likely to experience seizures, with up to 22% developing epilepsy. Additionally, as many as 64% of Alzheimer's patients show epileptiform discharges in EEG studies.[123,124]

Neuropathological Overlap:

A study involving 138 post-mortem brains of patients with chronic epilepsy revealed increased Alzheimer's-like pathology, particularly in individuals aged 50–65. Molecular

markers like tau and amyloid were found to increase seizure risk in experimental models.[125]

Epilepsy and Dementia Risk:

A meta-analysis demonstrated that individuals with epilepsy have double the risk of developing dementia compared to the general population. Early-onset epilepsy patients showed dementia rates similar to those who developed epilepsy later in life. Further research showed that childhood-onset epilepsy patients had increased amyloid deposits decades after the initial diagnosis.[126]

Treatment Implications:

A pilot study revealed that treating epileptiform discharges with levetiracetam improved cognitive function in Alzheimer's patients, hinting at the potential for therapeutic interventions targeting both seizures and cognitive decline. Disease-modifying treatments for neurodegenerative diseases may also help mitigate epilepsy and improve cognitive outcomes.[124,127]

Tau Pathology and Epilepsy:

Increased levels of hyperphosphorylated tau were found in epilepsy patients, particularly in those with drug-resistant temporal lobe epilepsy. Sodium selenate, a compound known to reduce hyperphosphorylated tau, has shown promise in animal models, offering potential for both reducing seizures and improving cognition.[128]

The presentation underscored the profound overlap between epilepsy, cognitive decline, and neurodegenerative diseases, emphasising the importance of addressing cognitive issues alongside seizure control in treatment strategies.

Monday 9th September 2024

MAIN SESSION: PAEDIATRIC EPILEPTOLOGY

NEW ROADS TO IMPROVE OUTCOME (AND TO LEAD TO ROME)

Chairs: Nicola Specchio (Italy); J Helen Cross (UK)

Tackling beyond seizure: moving from anti-seizure medications to disease modifying modifications

Stéphane Auvin (France)

The landscape of developmental and epileptic encephalopathies (DEE) and their treatments is complex. An epidemiological study showed a high prevalence of infantile spasms syndrome and other DEE in children aged ≤3 years.[129] When developing anti-seizure medications (ASMs), anti-epileptogenic treatment, or disease-modifying treatment (DMT), these aspects must be considered. ASMs present challenges such as non-adherence, not targeting underlying aetiology or non-seizure outcomes (cognition or behavior), and drug resistance. It is important to recognize while anti-epileptogenic treatment halts the progression of epilepsy, DMTs are helpful in treating or reducing the severity of epilepsy or comorbidities. As a result, both treatments may have different impact on both seizure- and non-seizure-related outcomes.

ASMs may be able to alter the course of epilepsy, which could complicate our knowledge of disease progression. For example, in a long-term prospective trial, patients with childhood absence epilepsy who received ethosuximide had significantly higher rates of complete remission compared with valproate at 5 and 10 years (76% vs 39%; p = 0.007).[130]

Pre-clinical studies show mechanisms that precede the onset of epilepsy such as ion-channel activation, early gene inflammation, oxidative stress, neurogenesis, network re-organisation, and gliosis. It can be difficult to find the best time for treatment, type, and dose of treatment for these mechanisms.

Targeted therapies are an option for treating pathogenic variants due to gene defects that cause epileptogenesis. Clinical trial designs will eventually need to adjust to targeted therapies and a preclinical phase to understand efficacy and safety, as well as the natural progression of disease, will be required. Phases I and II will be necessary to understand on-going effects, dose-escalation, and delayed treatment effects. The distinction between the mechanism of action of associated adenovirus and antisense oligonucleotide gene therapy will need to be considered when planning clinical trials for gene therapy.

Prevention, prediction, improvement: is the road still long?

Rima Nabbout (France)

The "4P" medical approach in the clinical management of patients with epilepsy stands for prediction, prevention, personalisation, and participation. Prediction plays a key role in pre-symptomatic diagnosis and disease outcome; it helps to determine the best course of therapy and risk of mortality. Lack of evidence on DMTs for tuberous sclerosis complex (TSC), Dravet syndrome, and PCDH-19 developmental and epileptic encephalopathy were highlighted by the recent work of Nabbout and colleagues who mapped epilepsy syndromes based on Advisory Committee on Heritable Disorders in Newborns and Children for rare disease criteria.[131] Every stage of clinical management of epilepsy involves the use of prediction tools, from classification of epilepsy based on the underlying aetiology,[132] to prognosis and treatment. A study showed that early electroencephalopathy (EEG)-based biomarkers differentiate between patients with epilepsy of infancy who experienced migrating focal seizures from other seizures.[133]

The EPISTOP trial incorporated a prospective EEG abnormality-based study and found that early EEG abnormality facilitated the prediction of neurodevelopmental outcomes, making diagnosis and treatment easier in patients with TSC.[134] Age at seizure onset is a crucial factor in prediction models for early diagnosis of certain epilepsies.[135]

Prevention is the cornerstone of clinical practice, and the EPISTOP trial demonstrates how to use the latent phase of epileptogenesis to prevent seizures. Primary prevention efforts such as managing central nervous system infections, providing appropriate prenatal and peripartum care, reducing the risk of traumatic brain injury (TBI), and using targeted therapies during epileptogenesis require further work. In addition, managing epilepsy requires adhering to sequential time and knowing when to act.

PARALLEL SESSION: PAEDIATRIC EPILEPTOLOGY

ARE DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHIES PROGRESSIVE DISEASES?

Chairs: Nicola Specchio (Italy); Elena Gardella (Denmark)

Cognitive functions in DEE: what the long-term observation tells us

Lieven Lagae (Belgium)

Professor Lieven Lagae's presentation focused on the cognitive and behavioral challenges in patients with developmental and epileptic encephalopathies (DEEs). He emphasized that cognitive problems often pose a greater burden on families than the seizures themselves, highlighting the need for a broader approach to DEE treatment that includes cognitive outcomes. Cognitive and behavioral issues are reported to be more distressing to families than seizures, with cognitive decline being a common challenge in DEE patients. Around one-third of all epilepsy patients develop intellectual disability (ID), while the rate is even higher in DEE patients, approaching nearly 100% in some cases.[136,137]

Contributing Factors to Cognitive Decline

Various factors contribute to cognitive impairment in DEE patients, including:

- Genetic etiology
- Age of epilepsy onset (earlier onset is associated with more severe ID)

- Seizure frequency and severity
- EEG abnormalities
- Medications (some anti-seizure drugs may have cognitive side effects)
- Social environment

Specific DEE Syndromes and Cognitive Outcomes

SCN2A Epilepsies: Cognitive decline over time is common in these patients, but not all show the same trajectory. Some exhibit intellectual disability even without significant seizures, suggesting that genetic factors alone may cause cognitive issues.[138]

STX-BP1: Approximately 72% of adult patients are non-verbal, and many have motor problems, reflecting the severe impact of the disorder on cognitive and motor function.[139]

SYNGAP1: Language problems are present in about 50% of adults with this syndrome, showcasing the broad spectrum of cognitive challenges these patients face.[140]

Tuberous Sclerosis Complex (TSC): Preventive treatments aimed at reducing seizures may not significantly improve cognitive outcomes. Early EEG abnormalities can predict future cognitive and autism-related outcomes, while other factors such as mutation type and seizure severity also play a role in intellectual disability at age 7.[141]

Dravet Syndrome: Patients show severe cognitive impairment, particularly after age 10. While some longitudinal studies indicate worsening cognitive function, a few patients remain stable or experience slight improvements over time. Speech impairment in Dravet syndrome correlates with seizure frequency, but this relationship is weaker for other cognitive domains, such as autism or ADHD.[142]

Treatment and Research Directions

EEG abnormalities detected in early infancy are predictive of future cognitive outcomes in several DEEs, making early monitoring critical. In some cases, cognitive impairment is driven more by genetic mutations than by seizure activity, indicating a need for therapies targeting genetic underpinnings.[142]

It was stressed the importance of long-term follow-up studies to better understand the cognitive trajectories in DEE patients and to inform treatment strategies that consider both seizure control and cognitive preservation. Prof. Lagae's presentation highlighted the complex, multifactorial nature of cognitive decline in DEEs and underscored the importance of considering both seizure management and cognitive development in treatment plans.

PARALLEL SESSION: SOCIAL ISSUES

DIFFICULT DISCUSSIONS IN NEWLY DIAGNOSED EPILEPSY

Chair: Natela Okujava

The impacts of newly diagnosed epilepsy – where are we now?

Venus Tang (Hong Kong)

Patients with newly diagnosed epilepsy have to cope with its various impacts. Physical effects include being limited in their activities, taking ASMs, and having a higher risk of falls and injuries. The unacknowledged effects of epilepsy include social isolation, stigma, and reduced employment and education opportunities. Other manifestations of newly diagnosed epilepsy include neurocognitive problems (e.g., memory issues) and psychological consequences (e.g., depression or anxiety). These elements are mutually dependent on each other (e.g., psychiatric comorbidities increase the risk of first seizure). An ongoing systematic review found that patients with newly diagnosed epilepsy reported psychological disturbances, deprived QoL, and stigma.

It is essential that both patients and clinicians are aware of the wide range of impacts of epilepsy. Raising awareness about the occurrence of mental comorbidities and of the misinformation about risks and medication side effects related to epilepsy are some ways to accomplish this goal. Self-management programs such as MOSES (Germany) and

SMILE (UK) enhance patients understanding of symptoms, coping strategies, QoL, self-management, and seizure knowledge. But there is a delay between the time of diagnosis and patients receiving information, which illustrates the necessity of providing patients with information from the outset of their diagnosis. In the absence of information at diagnosis, patients may resort to the internet, which at times may leave them confused and anxious with information overload. There is a disconnect between what patients want to know and what clinicians believe patients should know, as current self-management programs are not designed for patients with newly diagnosed epilepsy.

Some questions for future consideration posed by Dr Tang included: What information is necessary and desired by patients? To what extent should we educate patients? How can we help patients effectively apply their knowledge to self-care?

SUDEP counselling in newly diagnosed epilepsy – when, why and how?

Adam Strzelczyk (Germany)

Paediatric patients with epilepsy have poor rates of mortality – 30% of patients with symptomatic epilepsy report death by the age of 30 years. For 55% of patients with childhood-onset epilepsy, sudden unexpected death in epilepsy (SUDEP) was the most frequently reported cause of death.[143] In addition, SUDEP is the second most common cause of years of potential life lost, adding to the healthcare burden.[144] Since SUDEP and seizures are correlated, reducing seizure frequency is vital for preventing SUDEP.[145]

Only 2.7% and 3.3% of patients, respectively, were offered counselling for SUDEP and suicidal ideation in a study exploring attitudes towards SUDEP counselling of clinicians in Austria, Germany, and Switzerland.[146] Globally, including countries like the UK and USA, there was a similar pattern of low SUDEP counselling rates.[147] On further exploration, the most frequent reason for not providing SUDEP counselling to patients was that of raising concerns in patients (68.1%) and their family and carers (64.2%).[146] Conversely, adult patients and parents of children and young people with epilepsy expected clinicians to provide information on SUDEP.[148] It is not well established if counselling resulted in a change in patient behavior.[149]

When it came to factors that mattered most to patients, the ability to drive and work were ranked higher than mortality.[150] According to a recent study, around 70% of patients with epilepsy were unaware of SUDEP.[151] Most patients reported being either satisfied, or very satisfied, when asked about their level of satisfaction after receiving SUDEP information.[151] In addition, the vast majority of patients expressed a desire for SUDEP information to be made available to all patients with epilepsy.

Dr Strzelczyk recommended active management of epilepsy, supervision for patients with nocturnal seizures, and improving treatment compliance to reduce the frequency of seizures. He also advised seeking guidance from the NICE guideline on "Reducing the risk of epilepsy-related death, including SUDEP."[152]

When epilepsy starts at senior age – issues beyond the seizures

Natela Okujava (Georgia)

A case-study of a 64-year-old male patient was presented by Dr Okujava. At the age of 35, the patient had episodes of "derealisation" and subtle movements in his left hand, but epilepsy was not diagnosed. The patient was later diagnosed with epilepsy at the age of 63, when he experienced bilateral convulsive seizures from sleep which was confirmed on magnetic resonance imaging. Despite receiving carbamazepine at doses up to 1200 mg, he did not show improvement. His QoL was reduced due to severe snoring, daytime sleepiness, mood and personality changes, multiple medications, decline in cognitive function, inability to conduct his daily activities, and being prone to accidents. Furthermore, there were comorbidities such as increased body mass index, arterial hypertension, and diabetes. His condition also impacted his family and carers causing stress and poor sleep.

Dr Okujava and her team discussed the new treatment plan with the patient and his family. A multidisciplinary approach was used collaborating with an endocrinologist to review his

treatment for hypertension, diabetes, and obesity. Advice on non-pharmacological lifestyle modifications was given to the patient and his family members. At 1-year follow up, the patient showed improved sleep pattern, was more active, lost 15 kg in weight, and his convulsive seizures, diabetes, and hypertension were well controlled.

Dr Okujava recommended that the best course of action was to educate medical professionals about the high incidence and unique characteristics of epilepsy in elderly patients, collaborate as a multidisciplinary team to address multimorbidity, empower patients and caregivers with knowledge, develop patient-centred outcomes, and overcome the differences between the expectations of patients with epilepsy and their doctors.

Tuesday 10th September 2024

MAIN SESSION: BASIC SCIENCE

ADVANCED TARGETED GENE-THERAPY APPROACHES FOR EPILEPSY

Chairs: Eleanora Aronica (Netherlands); Aristea Galanopoulou (US)

General principles of gene therapy approaches

David Henshall (Ireland)

High rates of drug resistance in patients with epilepsy[153] and improved understanding of the genetic background of the disease have led to a more precise treatment approach. Gene therapy is already used for many conditions, but it is still under development for central nervous system (CNS) disorders.

The main method for delivery gene therapy involves viral vectors such as adeno-associated virus (AAV), lentivirus and herpes simplex virus, each having specific (dis)advantages. The most commonly used serotype is AAV9, which effectively targets the CNS and is relatively safe.

One type of gene therapy is to modify the viral DNA to include a gene of interest, which is then delivered to cells to express the desired protein. For focal epilepsies, the virus can be injected into the tissue that is generating seizures, while intravenous delivery may be required for generalized epilepsy.

For targeted gene therapy, viruses can be designed to bind only to specific cells, for example, inhibitory neurons in Dravet syndrome. In this case, mutated *SCN1A* can be "corrected" by inserting a sequence into the virus, which is then recognized by transcription factors that are only present in inhibitory neurons, but not in excitatory neurons. However, AAVs have limited cargo capacity due to small genome size, which limits gene replacement for large genes such as *SCN1A*. One potential approach may be the use of CRISPR-Cas9 machinery, which is a bacterial system inserted in a virus that is directed to a specific sequence within the genome, where it excises the mutated nucleotide sequence and replaces it with a non-mutated copy.[154]

Another approach is to target RNA with antisense oligonucleotides (ASOs), which are short oligonucleotides that can bind to specific RNA and modify gene expression. In the case of the mutated *SCN1A* gene, which produces a truncated form of the protein or no protein at all, ASOs can prevent premature stop codons, which leads to full protein production. Another potential approach is gene therapy dosing; however, strategies may be needed to vary the dose and timing of gene therapy.[155]

Several gene therapies are currently in clinical trials for epilepsy.[156-160] Examples are ASOs to boost *SCN1A* expression in human cell lines and mouse brain,[161] and ETX101, which uses a viral vector that delivers a transcription factor for *SCN1A* upregulation in Dravet syndrome.[162] Gene therapy might also be effective for non-genetic epilepsy, for example, by targeting microRNAs with ASOs to regulate gene expression.

Regarding safety, understanding the long-term safety of gene expression in the brain and optimal dosing of gene therapies is lacking, but AAV9 has demonstrated a generally good safety profile.[163-165]

Future possibilities include designing small molecule drugs which can selectively target RNA structures and regulate gene expression.[166,167]

Current Clinical Applications: gene therapy trials pipeline

Paul Boon (Belgium)

Despite advances in antiseizure medications (ASMs), the number of patients with drug-resistant epilepsy is unchanged. There are unmet needs and treatment gaps for patients with epilepsy.

Epilepsy surgery leads to improved outcomes, with over 70% of study participants achieving freedom from seizures after five years.[168] However, it is associated with limited access, a proportion of non-amenable patients (25%) and an inability to locate the epilepsy focus, among others. Furthermore, neuromodulation techniques (e.g., VNS, ANT-DBS) yield a responder rate of 25–70%, but rates of freedom from seizures are low (10–20%).[169]

Genetic therapies (etiological and somatic) are a novel approach to epilepsy treatment.[170] Etiological genetic therapies aim to modify gene expression to correct the underlying pathology. They are suitable for patients with rare monogenic syndromes, such as developmental and epileptic encephalopathies (DEEs). Strategies include gene supplementation in the case of loss-of-function (LoF) (e.g., AAV delivery of *SCN1A/B* for Dravet syndrome[171] or *CDLK5*[172]) and gene modulation (e.g., AAV delivery of CRISPR for *SCN1A* upregulation).[173-175] In the case of gain-of-function-related disease, antisense oligonucleotides (ASOs) have shown promise in conditions like Dravet syndrome, Angelman syndrome, Lafora disease and Unverricht-Lundborg disease.[171,176-179] For LoF-related diseases, ASOs can be used with TANGO (targeted augmentation of nuclear gene output) technology or an ASO-derived compound AntagoNAT, which both result in increased productive *SNC1A* transcripts, leading to reduced seizures and mortality in the Dravet mouse models.[171,180]

Somatic genetic therapies, used to suppress abnormal activity in epileptic networks, include neuropeptides such as neuropeptide Y (NPY), dynorphin and galadine.[181] AVV delivery in the hippocampus in experimental models showed a significant reduction in seizures and memory decline for all three molecules.[182-185]

Optogenetic and chemogenetic therapies are other strategies that are currently being investigated. Optogenetics modulates inhibitory or excitatory neurons with light-sensitive proteins (opsin injection) and light to decrease epileptic activity.[186-188] Chemogenetic therapy is on-demand/controllable modulation of epileptic circuits by using engineered receptors (e.g., DREADs), which are activated by specific ligands to control neuronal activity.[189-191]

Among currently tested biochemical autoregulatory gene therapy for focal epilepsy is eGluCl, which was shown to decrease neocortical focal seizures in rats, using pathological EC increases of glutamate as endogenous receptor activator.[192]

Several preclinical and clinical trials on genetic therapies for epilepsy are ongoing.[171] For Dravet syndrome, STK-001 (ASO) is being tested in the MONARCH and SWALLOWTAIL trials, showing promising reductions in seizure frequency (17–37% in 75% of patients) and improved cognitive and motor skills,[193] while ENDEAVOR is assessing ETX-101 (AAV-based vector).[175,193] For Angelman syndrome, GTX-102, an ASO reactivating the paternal *UBE3A* gene, has demonstrated positive early results.[178] Other compounds in clinical trials are non-integrating lentiviral vector for refractory neocortical epilepsy[194-196] and neuropeptides (GC01; NPY).[197]

PARALLEL SESSION: ADULT EPILEPTOLOGY

POST-STROKE EPILEPSY: PREDICTION, PREVENTION AND IMPLICATIONS FOR ICAP

Chairs: Eugene Trinka (Austria); Alla Guekht (Russian Federation)

Preventable epilepsies: focus on stroke and implications for IGAP

Alla Guekht (Russian Federation)

Professor Guekht highlighted prevention of neurological disorders and approach to specific neurological disorders as the pillars of Intersectoral Global Action Plan on Epilepsy

and Other Neurological Disorders (IGAP). The World Health Organization report on epilepsy estimates 25% of epilepsy cases to be potentially preventable.[198] A study by Guekht et al. found that the risk of mortality was significantly increased in patients with seizures and epilepsy post-stroke compared with controls ($p<0.001$).[199]

IGAP's integrated approach to neurological disorders with implications for research include identifying research priorities, facilitating collaboration, and understanding the disease-causing mechanisms. Studies have found lacrimal fluid to be a potential biomarker for epilepsy. Although there is a growing body of evidence on biomarkers and prediction models for epilepsy, there is scope for addressing uncertainties in post-stroke epilepsy (PSE) and understanding the role of artificial intelligence in prediction models.

In a collaborative study using optical coherence tomography-angiography, area and skeleton density of superficial and deep macular capillary plexuses were found to be decreased in patients with epilepsy treated with valproic acid. In addition, valproic acid was associated with higher risk of cardiovascular disease.[200] Despite the associated risks, valproic acid is the second most prescribed medication for epilepsy and requires further investigation.[201] Several studies have found autonomic dysfunction as a predictor of poor outcomes post-stroke. For example, one study reported that 90.9% of seizures were significantly associated with ictal autonomic dysfunction.[202] An on-going study found that early seizures were a significant risk factor for late seizures (Area under Curve = 0.85). Of note, was the elevated cortisol level as a predictor of mortality and late seizure ($p <0.001$, each) after TBI. Professor Guekht concluded by highlighting that IGAP had implications not only for clinical research, but also arrangement of care, and integrating with other neurological conditions as well as communicable and non-communicable diseases.

Drugs for prevention of post-stoke epilepsy

Eugen Trinka (Austria)

According to previous studies of anti-epileptic drugs, inappropriate study design and incorrect choice of drugs were the main reasons why seizure prevention post-stroke was not feasible.[203-205] As a result, biomarkers were investigated to develop new treatments for PSE prevention.[206] Stroke and seizure are major neurological conditions that affect patients worldwide and elderly patients are more likely to experience seizures,[207] with diagnosis often difficult due to existing comorbidities. The challenges of conducting antiepileptogenesis trials in the elderly population include selection of biomarkers, informed consent, choice of investigational agent and outcome parameters, long-term follow-up and adequate sample size.[208,209]

Future studies should make use of the SeLECT score, which serves as a prognostic model for prediction of late seizure after ischemic stroke.[210] A duration of 13 months was adequate to observe outcomes based on the latency duration of PSE.[211] Examples of potential drugs in the prevention of PSE include brivaracetam, ganaxolone, huperzine A, NAX-5055, and T-2000. A systematic review by Acton et al. found that statins were effective in the prevention of PSE.[212] Another potential drug class in the prevention of PSE was anti-hypertensive drugs (e.g., losartan).[213] A German cohort study found that angiotensin receptor blockers significantly decreased the incidence of epilepsy (HR, 0.77; 95% CI, 0.65–0.90).[214] However, further prospective studies are needed to explore the effectiveness of other drugs in the prevention of PSE.

The EGASIS trial found that diazepam lowered the incidence of seizures compared with placebo (0.9% vs 4.6%) in patients with cortical anterior circulation infarction.[215] Other ongoing efforts in antiepileptogenesis trials include a phase II trial of eslicarbazepine acetate (ESL)[216] and perampanel.[217] ESL was associated with a lower incidence of unprovoked seizures in stroke patients compared to placebo (3.3% vs 11.3%).[218] Other imaging and molecular biomarkers are under investigation and ASMs such as ESL may serve as antiepileptogenic drugs.

Wednesday 11th September 2024

PARALLEL SESSION: GENETICS

ASSESSING THE IMPACT OF GENETIC DIAGNOSIS IN CLINICAL CARE OF CHILDREN AND ADULTS WITH EPILEPSY

Chairs: Christian Korff (Switzerland); Gaeten Lesca (France)

Impact of Genetic Testing on Therapeutic Decision-Making in Childhood Onset Epilepsies

Allan Bayat (Denmark)

The genetics of epilepsy is highly complex and heterogeneous, with more than 1,000 genes involved.[219] Genetic epilepsies are quite common, occurring in at least 1 out of 2000 live births.[220]

Currently, conventional epilepsy management is largely empirical.[221] However, genetic testing, with comprehensive gene and exome panels available, has significantly improved the diagnosis of early-onset epilepsy and resulted in a more targeted treatment approach.

The impact of genetic testing on therapeutic decision-making in childhood-onset epilepsy has been demonstrated in a study on 188 children (most with developmental and epileptic encephalopathies [DEEs]).[222] After exome sequencing and other genetic analyses of patients with unsolved diagnosis (n=102), the total diagnosis rate was 50%. Results showed that 82% had single nucleotide variants (SNVs)/indels, 17% had copy number variations (CNVs) and 1% had ring chromosome 20 syndrome. Most mutations were found in *SCN1A* (Dravet syndrome), *TSC1/2*, *SCN2A*, *SCN8A*, *PCDH19* and *CDKL5*, with most associated with channelopathies that are treatable with available therapies. The precision therapy approach was possible for 53 patients, with 60% undergoing adjustments through genetic diagnosis. Notably, although only 12% achieved seizure freedom, 93% experienced more than a 50% reduction in seizures.

This study further showed that diagnostic yield depended on the age of onset: younger children (under two years of age) had higher diagnostic rates (60–70%).[222] Among children with solved diagnoses, seizures started early (approximately at six months), and they often had intellectual disability. For unsolved cases, the seizure onset was at around two years of age (mainly focal epilepsy), with fewer intellectual disabilities.

Recently, novel genetic mutations associated with epilepsy in children were described. A rare loss-of-function variant in the 5' region of the TRA2B gene was identified in neurodevelopmental syndrome.[223] Furthermore, gain-of-function (GoF) variants (Y141N and G239S) in the *KCNQ2* gene (coding for Kv7.2) were shown to cause a mild developmental delay with prominent language deficits but no neonatal seizures.[224] Amitriptyline effectively inhibited the current carried by Kv7.2 Y141N and G239S mutant channels, which resulted in improved motor, verbal and social behaviors in one patient during two years of treatment.

Cenobamate is a novel antiseizure medication that has been investigated as an add-on therapy for *SCN8A* GoF-associated DEEs.[225] In a study of 12 patients, all experienced a reduction in seizure burden, with the majority having more than a 90% reduction.

Genetic diagnosis impacts medical management for adult-onset epilepsies

Danielle Andrade (Canada)

mTORopathies are disorders associated with abnormal signaling in the mammalian target of rapamycin complex 1 (mTORC1), which results in changes in cell morphology, disorganized cortical lamination and neuronal hyperexcitability.[226-230] Various genes are implicated, such as *TSC1/2*, *DEPDC5*, *NPRL2/3* and *PTEN*, among many others. Diseases associated with mTORopathies include tuberous sclerosis complex (TSC), focal cortical dysplasia type II, hemimegalencephaly, megalencephaly, polymicrogyria, cortical heterotopia and hippocampal sclerosis.

Everolimus, an mTORC1 inhibitor that is used for treating TSC and reducing tuber size, also demonstrated seizure reduction in pediatric patients with treatment-refractory seizures associated with TSC in the phase III EXIST-3 study.[231] A case series further reported its potential benefit for epilepsy related to *DEPDC5* mutations, particularly in loss-of-function variants.[232] *DEPDC5* mutations were also shown to be associated with sudden unexpected death in epilepsy (SUDEP).[233,234]

Resective surgery is an option for epilepsy treatment and requires comprehensive pre-surgical evaluation, including seizure monitoring and imaging. Data show that (germline) genetic testing is increasingly applied to pre-surgical epileptic patients.[235] A retrospective study demonstrated that patients with mTORopathies were more likely to undergo surgery compared with those with channelopathies,[236] which was also reported in a systematic review.[237] Based on this, genetic findings should not preclude presurgical evaluation or epilepsy surgery and genetic variations can guide surgical decisions.

The PCDH19 (protocadherin-19) clustering epilepsy (initially related to epilepsy and mental retardation limited to females [EFMR]),[238,239] is a condition associated with recurrent fever-induced clusters of seizures in infancy and psychiatric comorbidities in later life.[240] Similarly, 22q11.2 syndrome is linked to schizophrenia/schizophrenia spectrum disorders in up to 25% of patients; notably, clozapine induces seizure in a high proportion of these patients.[241-243]

Does the genetic diagnosis with DEE matter?

Francesca Bisulli (Italy)

The incidence of developmental epileptic encephalopathies (DEEs) in adults is unknown, but the number of adults with early-onset monogenic epilepsy is increasing as improved care prolongs the survival of these patients. Approximately 40% of DEEs are monogenic[244] and over 70% of monogenic epilepsy patients require neurological care in adulthood.[245]

The genetics of DEEs in adulthood is poorly understood, as genetic testing was not commonly performed in older patients when they were children, which means that many adults with DEEs have no genetic or etiological diagnosis. This group of patients is referred to as the "lost generation" (born before 2013) because they did not receive genetic testing with array CGH or NGS in childhood, which could have provided an accurate diagnosis and potentially improved neurodevelopmental outcomes.[246,247]

Challenges for patients with late diagnoses include inconclusive and contradictory results from early clinical records, vague early symptoms and missing crucial medical information, with phenotype obscured by comorbidities and antiepileptic medication side effects. Notably, adult neurologists are often less confident than pediatric neurologists (~10% vs ~90% confidence) in diagnosing and managing DEEs, which often leads to delayed or wrong diagnoses.[248]

Genetic diagnosis is complex due to the rapid pace of discoveries. There are over 800 epilepsy-related genes and 90% are linked to DEEs.[247] NGS has a diagnostic yield of 25–50%, which is higher in patients with brain malformations, early-onset epilepsy and dysmorphisms.[249-251] Data showed that the median diagnostic delay is around 40 years, but late diagnosis can still impact the clinical management for many patients.[251]

In addition to NGS, karyotyping and CGH arrays are important in identifying genetic abnormalities, such as ring chromosome 20 syndrome and pathogenic copy number variations (present in up to 20% of patients,[250,252,253]) respectively. Testing mitochondrial DNA and the genes coding for inborn errors of metabolism[254] is also recommended for adults with DEE of unknown etiology.

Although late genetic diagnosis may be frustrating, it can end the diagnostic odyssey for patients and families and allows genetic counseling, as well as improves clinical management and our knowledge about the disease.

CONGRESS HIGHLIGHTS

Chairs: Matthew Walker (UK); Nicola Specchio (Italy)

Pediatrics highlights

Nicola Specchio (Italy)

Professor Nicola Specchio presented key insights from pediatric-focused sessions at the epilepsy conference, with an emphasis on improving outcomes for children with developmental and epileptic encephalopathies (DEE).

Epileptogenesis in DEE

The presentation explored the underlying mechanisms of epileptogenesis in DEE, focusing on synaptic plasticity, GABA dysregulation, functional connectivity, inflammation, and mTOR hyperactivation. A central debate was whether developmental impairments in these conditions occur before or after epilepsy onset. Evidence suggests that, in most cases, development is affected before the onset of epilepsy. Basic science studies, particularly those in Dravet Syndrome, show that early disruptions in dendritic harmonization contribute to developmental delays.

Surgical Timing and Outcomes

Early surgical intervention in pediatric epilepsy patients leads to better developmental outcomes. Children who undergo surgery with an epilepsy duration of less than two years show an improved developmental trajectory compared to those with a longer duration of uncontrolled seizures.

Disease Modification and Prevention

The potential for disease modification through early intervention was discussed, with ongoing studies examining how modifying disease progression might improve long-term outcomes. Prevention and early prediction of epilepsy onset were also explored as strategies to enhance outcomes in early-onset epilepsy cases.

Progression of Disease in DEE

Professor Ingrid Scheffer's talk on the genetic mechanisms behind disease progression provided valuable insights into how specific genetic mutations drive disease progression in DEE. Work on EEG features highlighted the importance of correlating EEG patterns with cognitive and developmental improvement in children with DEE.

Care in Underprivileged Areas

Professor Joe Wilms presented on epilepsy care initiatives in underprivileged regions, focusing on improving care for children in Africa who lack access to advanced epilepsy treatments.

Additional Platform Sessions

Several sessions covered neuroimaging and neurophysiology, specifically in pediatric epilepsy, highlighting new approaches to imaging and understanding brain connectivity in children with epilepsy.

CLINICAL HIGHLIGHTS

Laura Tassi (Italy)

Dr. Laura Tassi presented an extensive review of 31 clinical sessions, addressing various domains in epilepsy research and treatment. Her presentation provided insights into neurophysiological, neuroimaging, and genetic aspects of epilepsy, as well as related psychiatric and gender issues.

Neurophysiology

The current use of neurophysiological techniques, particularly their integration with imaging methods such as automated imaging guidance (AIG) and invasive monitoring was discussed. A key point was the differentiation between interictal (non-seizure) and ictal (seizure) EEG patterns, which are crucial for epilepsy diagnosis. Neurophysiological methods are also being applied in other pathologies, such as post-cardiac arrest conditions.

Neuroimaging

Advances in artificial intelligence (AI) have enhanced imaging capabilities, leading to better detection of epileptic zones and improved visualization of brain connectivity in patients with epilepsy.

Epidemiology Findings

Limited coverage was given to epidemiology, though an interesting discussion was raised about gelastic seizures (involving laughing and smiling) and how they are organized in the brain. The presentation also touched on the comparison of epileptic events during sleep with other sleep disturbances, as well as the definition of focal seizures based on electrical and clinical criteria.

Genetics

Dr. Tassi addressed the importance of individualized genetic testing in epilepsy, which allows for more targeted treatments based on specific mutations.

Psychiatry and Gender Issues

There is an increasing focus on psychiatric complications in older epilepsy patients, which was highlighted as a growing public health concern. Gender issues in epilepsy were also briefly discussed, but did not discuss the specific challenges presented.

Autoimmune Diseases and Comorbidities

Autoimmune diseases and epilepsy comorbidities were briefly mentioned as areas of clinical significance requiring further exploration in research and treatment approaches.

Contributions from Young Researchers

The presentation noted the growing contributions of young researchers in fields such as the gut-brain axis, the application of artificial intelligence in epilepsy treatment, the impact of climate change on epilepsy patients, and studies on acute symptomatic seizures.

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