

EDITORIAL

Epilepsy: An integrated perspective

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The International League Against Epilepsy defines epilepsy as a brain disorder characterized by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition.¹ This definition marks a significant conceptual shift, moving beyond the mere occurrence of seizures to embrace a broader and more systemic view of the disorder.

In line with this definition, epilepsy can be understood as a spectrum disorder, manifesting not only through recurrent seizures but also through a wide range of psychiatric, medical, and cognitive comorbidities, which profoundly affect the individual's overall functioning. The etiological underpinnings of epilepsy are multifactorial and, in many cases, remain only partially understood. This etiopathological complexity contributes to the variability of clinical presentations and the unpredictability of disease progression. Therefore, a global assessment plays a central role in characterizing the functional profile of individuals with epilepsy. This process should include the electroclinical characterization of seizures, advanced imaging assessments and genetic and metabolic investigations aimed at elucidating the etiology of the disorder, the identification of cognitive and psychological impairments, the evaluation of more effective antiepileptic drugs with minor adverse effects, and the planification of tailored neurorehabilitation interventions.^{2,3}

Current areas of interest in clinical epilepsy research focus on: the study of different etiopathogenesis of its various forms, attempting to clarify the role of comorbidities that may arise and complicate the clinical picture and prognosis; the development of more specific and effective antiepileptic treatments, both pharmacological and non-pharmacological (including surgical interventions and neuromodulation); and the identification of alternative diagnostic and monitoring methodologies, primarily through advancements in imaging techniques, deep learning, and artificial intelligence.

The special issue "Advances in the pathogenesis, diagnosis, and treatment of epilepsy" for the *Advanced Neurology* aimed to collect new evidence about the genetic and environmental etiological factors of epilepsy, new diagnostic strategies, new developments in management and treatment, as well as innovative insights on the neuropsychological and cognitive implications of epilepsy.

De León-Ojeda *et al.*⁴ conducted a study to unravel the genetic contributions to neurodevelopmental disorders frequently comorbid with epilepsy through a descriptive observational analysis of 24 pediatric patients and 30 relatives from Mexico. All patients underwent comprehensive clinical evaluations and personalized next-generation sequencing panel testing. A definitive or suspected genetic diagnosis was achieved in

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more than half of the cases. The most frequent epilepsy comorbidities were communication disorders, autism spectrum disorder, and intellectual disability. Importantly, pathogenic and likely pathogenic variants were detected in genes such as *SYNGAP1*, *CDKL5*, *MECP2*, *PTEN*, and *PNPT1*. The findings highlight the heterogeneity and complexity of the genetic landscape underlying neurodevelopmental disorders and epilepsy and emphasize the critical role of genetic testing in improving diagnostic accuracy and guiding individualized therapeutic strategies.⁴

Similarly, Teng *et al.*⁵ in their literature review highlighted the critical role of the mammalian target of rapamycin (mTOR) pathway in epileptogenesis. Dysregulated mTOR signaling, driven by pathogenic variants in positive or negative regulators, underlies a broad spectrum of disorders called mTORopathies and GTPase-activating protein activity towards RAG complex (GATORopathies). These conditions are characterized by cortical malformations, neuronal hyperexcitability, and high seizure susceptibility. Conventional antiseizure drugs mainly act symptomatically on ion channels or neurotransmitter balance, mTOR inhibitors such as rapamycin and everolimus have shown disease-modifying and anti-epileptogenic effects in both preclinical and clinical studies. The review concludes that early, sustained, and individualized inhibition of the mTOR pathway constitutes a promising precision-therapy strategy in epilepsy, with the potential not only to achieve seizure control but also to modify the trajectory of disease progression.⁵

Conversely, Shrivastava *et al.*⁶ examined a non-genetic cause of epilepsy—traumatic brain injury—which is a leading cause of neurological disability, with post-traumatic epilepsy representing one of its most debilitating outcomes. Beyond epilepsy, traumatic brain injury often results in cognitive deficits, psychiatric disorders, and motor impairments, which collectively reduce patients' quality of life and complicate rehabilitation. Conventional antiepileptic drugs remain the cornerstone of management; however, their limitations highlight the urgent need for alternative strategies. Advances in precision medicine, neurostimulation techniques, stem cell therapy, neuroprotective agents, and gene-based approaches hold promise for addressing drug-resistant cases. The review concludes that a comprehensive, multidisciplinary approach integrating early diagnosis, biomarker and imaging-based prognostic tools, modern pharmacological and neuromodulatory therapies, and selected traditional practices are essential for improving outcomes in epilepsy related to traumatic brain injury.⁶

A wide range of risk and protective factors are implicated in the pathogenesis of epilepsy and its clinical presentation.

Nevertheless, the underlying mechanisms remain only partially elucidated and continue to represent a major focus of ongoing scientific investigation. Vahhabzadeh *et al.*⁷ demonstrated that regular physical exercise significantly increases serum high-density lipoprotein (HDL) and Vitamin D levels in epileptic conditions, thereby contributing to the preservation of hippocampal neurons and mitigating seizure-induced damage. The observed reduction in neuronal degeneration, coupled with the systemic benefits of increased HDL and Vitamin D, suggests that exercise may serve as an accessible and cost-effective adjunct to conventional antiepileptic therapies. Future research is warranted to elucidate the precise molecular mechanisms underlying these protective effects and to determine their translational applicability in human epilepsy.⁷ However, Ketema *et al.*⁸ focused on investigating risk factors of seizures, underscoring that the vast majority of patients with epilepsy in Addis Ababa are able to identify seizure-precipitating factors, with emotional stress, missed anti-epileptic doses, and inadequate sleep emerging as the most frequent triggers. Incorporating structured screening tools and engaging family members in counseling may enhance adherence to non-pharmacological interventions, thereby reducing seizure burden and improving overall quality of life.⁸

The exploration of new diagnostic methodologies and therapeutic strategies for epilepsy constitutes a particularly prolific field of research. Nasef *et al.*⁹ assessed the effectiveness of multiple machine learning models: Dense Neural Networks, Convolutional Neural Networks, and Light Gradient Boosting Machine, in classifying epileptic and non-epileptic electroencephalogram signals. Using a publicly available dataset, the models were trained and evaluated through accuracy metrics, learning curves, confusion matrices, and receiver operating characteristic (ROC) analyses to examine both performance and generalizability. The results indicated that Convolutional Neural Networks consistently outperformed alternative approaches, marked by higher accuracy achieved in classification. Their ability to capture spatial and temporal dependencies in EEG signals, coupled with stable convergence patterns, underscores their robustness for clinical applications.⁹ Shrivastava *et al.*¹⁰ comprehensively reviewed the current evidence on drug-resistant epilepsy, with particular emphasis on animal models, mechanisms of resistance, and innovative therapeutic strategies. Importantly, emerging methodologies such as optogenetics, chemogenetics, and advanced imaging are reshaping the landscape of preclinical epilepsy research. These tools enable unprecedented precision in mapping seizure circuits and assessing interventions in real time. The authors stress the need for integrative strategies that

combine insights from experimental models with real-world patient data. Incorporating omics technologies and humanized models is considered essential for identifying individualized drug targets and tailoring therapies.¹⁰

Evidence collected by this Special Issue underlines that significant obstacles persist in translating preclinical discoveries into clinical benefit *and that significant efforts are needed to achieve* a realistic path toward personalized and more effective treatments to profoundly improve the quality of life of individuals living with epilepsy and its comorbidities.

Conflict of interest

Michele Roccella is an Editorial Board Member of this journal and serves as the Guest Editor of this special issue. All authors declared that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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