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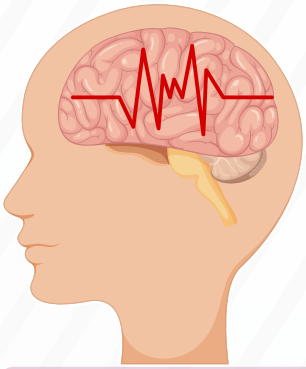
Innovative Approaches and Insights on Epilepsy Treatment: A Comprehensive Overview

Understanding early onset, clinical features, and treatment advances of epilepsy



Epilepsy is a neurological disorder characterised by recurrent and unprovoked seizures[1]

Epilepsy syndromes constitute a group of clinical characteristics distinguished by[1]:

- Seizure type(s)
- Age at onset
- Electroencephalography findings
- Genetic risk factors and history
- Prognosis and treatment response

- Epilepsy affects 1% of the population[1]
- Notably, a substantial proportion of epilepsy syndromes have a childhood onset, which significantly impacts brain development[1]
- Various antiseizure medications (ASMs) have been approved for the treatment of epilepsy[1]
- However, one-third of patients experience drug refractory epilepsy (DRE) with continued seizures despite trials of two or more ASMs[1]

There is a pressing need for novel therapeutic agents and treatment strategies to ensure:

- Effective seizure control
- Minimal side effects
- Improved quality of life of patients

The critical window: early diagnosis and treatment interventions in epilepsy

Age at seizure onset is a key characteristic of epilepsy syndromes and is influenced by multiple factors[2]

Potential determinants[1,2]

- Age-related gene expression
- Postnatal brain maturation: myelination, sulcation, and synaptic pruning
- Pathology, anatomical location, and size of the lesion
- Genetic aetiology
- Functional network connectivity
- Immune and hormonal factors
- Environmental and lifestyle influences

Understanding the factors that influence age at onset can aid early detection and treatment initiation

However, elucidating the multifactorial influences can be challenging given the heterogeneity of epilepsy syndromes[2]

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Bottom-of-sulcus dysplasias (BOSDs) and seizure onset

BOSDs are pathologically, genetically, and morphometrically homogeneous focal lesions[2]

For patients with small brain lesions that are positive on magnetic resonance imaging (MRI), a younger age at seizure onset is observed, which is:

Associated with:

- Greater lesion volume
- Pathogenic germline mammalian target of rapamycin pathway variants
- Default mode network overlap and connectivity to cortical and subcortical regions

Not associated with:

- Seizure subtype
- Postnatal cerebral maturation
- Location within the primary cortex
- Position along the caudal–rostral axis
- Sulcal depth
- Overlap with sensorimotor cortex or networks

A larger mass of epileptogenic tissue may result in significant local epileptogenesis and network disruption contributing to early age onset of seizures[2]

Advances in gene sequencing have uncovered pathogenic mechanisms underlying paediatric-onset epilepsies that can[3]:

- Aid precise molecular diagnosis
- Enable personalised treatment
- Reduce polytherapy-related side effects

Retrospective analysis of genetic variants in patients with paediatric-onset epilepsy[3]

Pathogenic: 13%

Likely pathogenic: 11%

Variants of unknown significance: 25%

Unlikely pathogenic and non-pathogenic: 51%

Patients with a definitive molecular diagnosis show typical clinical features, including[3]:

- Early-onset epilepsy
- Presence of neurological deficits: psychomotor delay or cognitive defects
- Developmental delay
- Abnormalities in brain MRI

Molecular diagnosis can help identify patients who are likely to benefit from personalised treatments[3]

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Treatment approaches to managing DREs

Periventricular nodular heterotopia (PVNH) is a neuronal migration disorder that can result in drug-resistant seizures[4]

Treatment of PVNH is challenging due to[4]:

- Adjacent malformed cortical structures
- Functional connectivity of heterotopic nodules with other nodules in the same and the contralateral hemisphere
- Deep location close to critical subcortical structures
- Large lesions

Magnetic resonance-guided laser interstitial thermal therapy (MRgLITT) enables precise targeting of PVNH[4]

However, the association between the extent of ablation and treatment outcomes remains unclear[4]

Retrospective analysis of patients with PVNH-associated DRE who underwent MRgLITT[4]

Patient cohort	Seizure freedom rate (%)
Unilateral PVNH with no other lesions	80
Bilateral diffuse disease and seizure onsets not localised to PVNH	63
Bilateral PVNH	50

PVNH ablation (associated with) good surgical seizure outcomes[4]

MRgLITT has the potential to transform the treatment of PVNH-associated epilepsy and other challenging DREs[4]

- Corpus callosotomy (CC) is a palliative surgical approach for the treatment of DREs in patients with significant neurological impairments[5]
- While CC is associated with substantial seizure reduction, it is an infrequently used therapeutic option, due to the risks associated with an invasive open craniotomy[5]

Emerging minimally invasive surgical approaches can reduce the complications associated with open surgery[5]

Prospective observational cohort study[5]

The majority of procedures in paediatric patients undergoing CC for DRE included:

57%: traditional open craniotomy

20%: LITT

22%: mini-craniotomy/ endoscopy

Open versus minimally invasive surgery[5]

No significant difference in favourable surgical outcomes

Similar length of hospital stay

Greater blood loss and intra-operative use of blood products

Greater postoperative complications and 30-day readmission rate

Minimally invasive CC approaches offer similar seizure outcomes as open surgery with fewer complications; their adoption can, thus, improve the use of palliative surgery as an early intervention[5]

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New horizons in epilepsy treatment: achieving seizure freedom with new-generation ASMs

- New-onset seizures require immediate treatment to minimise their long-term impact[6]
- ASMs work by decreasing the electrical activity of the brain via different mechanisms[1,6]
- Levetiracetam, an intravenous ASM, has emerged as an effective and safe first-line therapy[6]
- However, compounding and intravenous piggyback (IVPB) infusion can delay its delivery and impact seizure outcomes[6]
- While undiluted IV push (IVP) reduces time to administration, its efficiency and safety remain unclear[6]

Retrospective cohort study on patients with acute or suspected seizures[6]

Median time to administration of a loading dose of >2,000 mg

IVP: 12 minutes versus IVPB: 38 minutes

Similar rates across both groups

- Adverse events
- Intensive care unit admission
- Rescue medication requirement

Levetiracetam loading doses of up to 4,500 mg given as IVP significantly reduced time to the administration versus IVPB, with similar adverse effects[6]

Use of multiple ASMs warrants the need for understanding drug interactions and potential adverse effects

Cenobamate (CNB) is a novel ASM recently approved for the treatment of epilepsy[7]

However, its dual action of inducing and inhibiting hepatic enzymes can affect the metabolism of other ASMs[7]

While CNB is concomitantly administered with clobazam (CLB), their pharmacokinetic interaction is unclear[7]

Retrospective study assessing patients co-treated with CNB and CLB[7]

Measurement of serum concentration of CLB and its metabolite N-desmethylclobazam (NCLB)

Adjuvant administration of CNB with CLB[7]

- Significant reduction in seizure frequency
- Increase in serum concentration of NCLB
- Increased fatigue-dose reduction of CLB led to improvement in fatigue

Co-medication with different ASMs can improve treatment efficacy[7]

Therapeutic drug monitoring and dose titration can help mitigate unwanted side effects[7]

Key messages

Emerging surgical interventions and novel therapeutic agents hold significant promise in the treatment of DREs

Tailoring treatments based on patient-specific characteristics can help reduce side effects and improve treatment outcomes

References

1. Stafstrom, C. E., & Carmant, L. (2015). Seizures and epilepsy: an overview for neuroscientists. *Cold Spring Harbor Perspectives in Medicine, 5*(6), a022426.
2. Macdonald-Laurs, E., Warren, A. E. L., Leventer, R. J., & Harvey, A. S. (2024). Why did my seizures start now? Influences of lesion connectivity and genetic etiology on age at seizure onset in focal epilepsy. *Epilepsia, 65*(6), 1644–1657.
3. Castellotti, B., Ragona, F., Freri, E., Messina, G., Magri, S., Previtali, R., … & DiFrancesco, J. C. (2024). Next-generation sequencing in pediatric-onset epilepsies: analysis with target panels and personalized therapeutic approach. *Epilepsia Open, 9*(5), 1922–1930. (2024).
4. McCormack, R. M., Chandran, A. S., Lhatoo, S. D., Pati, S., Li, Z., Harris, K., … & Tandon, N. (2024). Laser ablation of periventricular nodular heterotopia for medically refractory epilepsy. *Annals of Neurology, 96*(6), 1174–1184. (2024).
5. Hansen, D., Shandley, S., Olaya, J., Hauptman, J., Auguste, K., Ostendorf, A. P., … & Perry, M. S. (2023). A multi-center comparison of surgical techniques for corpus callosotomy in pediatric drug-resistant epilepsy. *Epilepsia, 65*(2), 422–429.
6. Koons, M., Koehl, J., Johnson, R., Rosenthal, E. S., & Webb, A. J. (2024). Efficiency and safety of high-dose undiluted intravenous push levetiracetam loading doses compared to intravenous infusion in seizing patients: a retrospective cohort study. *Epilepsia, 65*(10), 2888–2896.
7. Elakkary, S., Hagemann, A., Klimpel, D., Bien, C. G., & Brandt, C. (2023). A retrospective non-interventional study evaluating the pharmacokinetic interactions between cenobamate and clobazam. *Epilepsia, 64*(4).

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