frontiers | Frontiers in Neurology

TYPE Editorial
PUBLISHED 29 March 2023
DOI 10.3389/fneur.2023.1185710

OPEN ACCESS

EDITED AND REVIEWED BY
Fernando Cendes,
State University of Campinas, Brazil

*CORRESPONDENCE
Vineet Punia
puniav@ccf.org

SPECIALTY SECTION
This article was submitted to Epilepsy, a section of the journal Frontiers in Neurology

RECEIVED 13 March 2023
ACCEPTED 20 March 2023
PUBLISHED 29 March 2023

CITATION
Punia V, Galovic M, Chen Z and Bentes C (2023) Editorial: Acute symptomatic seizures and epileptiform abnormalities: Management and outcomes. *Front. Neurol.* 14:1185710. doi: 10.3389/fneur.2023.1185710

Editorial: Acute symptomatic seizures and epileptiform abnormalities: Management and outcomes

Vineet Punia[1]*, Marian Galovic[2], Zhibin Chen[3,4] and Carla Bentes[5,6,7]

[1]Epilepsy Center, Cleveland Clinic, Cleveland, OH, United States, [2]Department of Neurology, Clinical Neuroscience Center, University Hospital and University of Zürich, Zürich, Switzerland, [3]Department of Neuroscience, Central Clinical School, Monash University, Melbourne, VIC, Australia, [4]Department of Medicine – Royal Melbourne Hospital, University of Melbourne, Parkville, VIC, Australia, [5]Reference Centre for Refractory Epilepsies (Member of EpiCARE), Hospital de Santa Maria-CHULN, Lisbon, Portugal, [6]Department of Neuroscience and Mental Health (Neurology), Hospital de Santa Maria-CHULN, Lisbon, Portugal, [7]Centro de Estudos Egas Moniz, Faculdade de Medicina da Universidade de Lisboa, Lisbon, Portugal

KEYWORDS

anti-seizure medication (ASM), acute symptomatic seizure, PASS clinic, epileptogenesis, continuous EEG (cEEG)

Editorial on the Research Topic
Acute symptomatic seizures and epileptiform abnormalities: Management and outcomes

Every brain can produce an epileptic seizure. A key distinction is whether it is provoked or unprovoked. This dichotomy alludes to the identification of a temporally-associated etiology. When it is present at the time of, or immediately preceding, a seizure, they are called acute symptomatic seizures (ASyS). The insult-to-ASyS time window is etiology-dependent, ranging from 24 h to 7 days and longer (1). Conceptually, the idea of seizure risk reduction after reversing underlying etiology is quite appealing. However, most ASyS are secondary to a non-reversible etiology, such as acute brain injuries (2), and exert a far more significant impact than traditionally appreciated. Assumptions and assertions about these "transitory" events have prevented systematic investigations into ASyS management, outcomes, and its natural history determination. The most glaring example underlies its fundamental defining feature—seizures within 7 days of acute brain injuries—proposed initially for "epidemiological studies" (1), which now pervades clinical practice. While seizures after the arbitrarily chosen 7 days have different outcomes than ASyS (3), emerging data suggest that ASyS after 3 days of injuries like stroke have similar implications (4). Needless to say, it is time to rethink ASySs and their standing in clinical epileptology.

Convulsive ASyS are ubiquitous in clinical practice and, depending on geographical location, account for 40–50% of all afebrile seizures (5). Convulsive ASyS, including ones from metabolic insults, undoubtedly increases the risk of epilepsy development (epileptogenesis) (5, 6). Prognostic models for symptomatic epilepsy development find ASyS contributing the highest risk among predictors of epileptogenesis (7, 8). As a corollary to the classic dictum of *seizure begets seizure* (9), if a brain can generate a seizure (ASyS) once, it is easier for it to produce an unprovoked, remote symptomatic seizure as well, i.e.,

remote symptomatic epilepsy (10). In other words, ASyS may be a marker of a lower seizure threshold in an individual.

The risk of symptomatic epilepsy after ASyS in stroke patients is 33% (3), precisely similar to the risk of developing epilepsy after a first unprovoked seizure (11). The SeLECT score, a prognostic model for ischemic stroke, predicts more than 60% risk of epilepsy development within a year of ASyS in patients with MCA cortical stroke and more than 3 NIHSS (7), suggesting that epilepsy can be diagnosed at the time of ASyS in some patients (10). These high seizure recurrence risk predictions can have socio-economic ramifications for patients, including driving restrictions.

Convulsive ASyS represents only "*the tip of the iceberg*" when it comes to acute epileptogenic activity after brain injuries. ASyS prevalence is higher in the era of continuous EEG (cEEG) monitoring because most are non-convulsive, i.e., electrographic seizures, during hospitalization (12, 13). In addition, epileptiform abnormalities (EAs) such as lateralized periodic discharges (LPDs), lateralized rhythmic delta activity (LRDA), etc., which significantly increase ASyS risk, are present in 25–40% of patients undergoing acute EEG (14, 15). Like convulsive ASyS, these electrographic findings also increase epilepsy development risk (14, 16–18). Based on this evidence, it is no exaggeration that ASyS and acute EAs may represent the earliest stage of epileptogenesis. Hence, ignoring ASyS and EAs as an epiphenomenon of acute injury is a heavy loss of opportunity for enhancing our understanding of epileptogenesis biomarkers and targets for testing anti-epileptogenic therapies—the holy grail of epilepsy care.

Mortality after ASyS is nine times higher than unprovoked seizures, with a 30-day case fatality of 20% (3, 19). Primary ASyS prophylaxis using anti-seizure medications (ASMs) is recommended after brain injuries, like trauma (20), but not stroke and hemorrhages (21, 22). Some experts recommend ASM prophylaxis after ASyS in intracerebral hemorrhage (ICH) (22) or after "recurrent" ASyS in ischemic stroke (21). In contrast, some organizations recommend against secondary ASM prophylaxis after ischemic stroke (23), and we lack data to support its use after infections (24). Nonetheless, real-world data shows that ASyS and EAs are frequently treated with ASMs during hospitalization, and patients are discharged on them (25–27). While 20% ASyS present as status epilepticus (6), 100% are treated with a status epilepticus management algorithm. The costs and benefits of this treatment strategy for ASyS remain unknown. The *unknowns* abound in this sphere—convulsive vs. electrographic ASyS management, wisdom of prophylactically treating EAs to prevent ASyS, duration of inpatient therapy, and need for discharging patients on ASMs after ASyS—are all unknowns. The latter does not show any benefit in neonates (28). Due to a lack of data guiding optimal ASM duration in adults, a majority continue ASMs several months to years after hospital discharge (29, 30). There is a large variability of expert recommendation on the duration of ASM continuation after ASyS and EAs ranging from months to years (31, 32). In the absence of anti-epileptogenic therapies, there is an acute need for developing evidence-based management strategies in this patient population.

This research collection aims to collate the latest research and review articles concerning ASyS and EAs, their implications, and management. Fatima et al. found that the evolution of LPD's amplitude over time in a patient correlates with seizure risk. Martinez et al. found that nearly a quarter of suspected ASyS patients undergoing cEEG monitoring have the poorly understood phenomenon of stimulus-induced, rhythmic, periodic, or ictal discharges (SIRPIDs), especially common in acute systemic illness, and may correlate with poor outcomes. Pan et al. report that a lower partial pressure of carbon dioxide ($PaCO_2$) in intracerebral hemorrhage patients could be associated with an increased risk of hyperacute (<24 h) ASyS. Yu et al. found that late symptomatic seizures (>12 months), rather than ASyS after moderate to severe traumatic brain injury, are associated with unfavorable long-term (5 years) functional outcomes. Tako et al. report that the severity of large arterial vessel occlusion ischemic stroke, based on the NIHSS at 24 h after admission, has a small but significant association with subsequent ASyS. Germeraad et al. explore the age-old question of primary ASyS prophylaxis in the unique setting of hematopoietic stem cell transplantation with busulfan conditioning and report that phenytoin use may cause more harm than benefit and hence recommend against it. Asnakew et al. report that in a specific Ethiopian region and community, illiteracy is the primary driver of people's attitude and care toward people with seizures, ASyS, or otherwise. Sharma et al. provide a comprehensive, concise, and clinically helpful review of the role of cEEG in managing patients with suspected ASyS, including challenges and new opportunities for its widespread use. Kong and Marawar address the knowledge gap about the often ignored, highest-risk for ASyS demographical segment—the older adults. Yoo reviews the current literature on BIRDs (Brief Potentially Ictal Rhythmic Discharges) that have a high degree of association with ASyS and status epilepticus and subsequent outcomes.

We will be remiss not to point out the lack of articles that can guide us on ASyS and EA management in the collection. However, it merely reflects the malaise toward ASyS management research in the neurological community. A phenomenal boost to help overcome this apathy would be to define etiology-specific ASyS using multimodal biomarkers, which will be a big step toward improving management, prognosis, and understanding epileptogenesis.

Author contributions

VP, MG, ZC, and CB contributed to the conception of the editorial. VP wrote the first draft of the manuscript. All authors contributed to the manuscript revision, read, and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated

organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Beghi E, Carpio A, Forsgren L, Hesdorffer DC, Malmgren K, Sander JW, et al. Recommendation for a definition of acute symptomatic seizure. *Epilepsia.* (2010) 51:671–5. doi: 10.1111/j.1528-1167.2009.02285.x

2. Annegers JF, Hauser WA, Lee JR, Rocca WA. Incidence of acute symptomatic seizures in Rochester, Minnesota, 1935-1984. *Epilepsia.* (1995) 36:327–33. doi: 10.1111/j.1528-1157.1995.tb01005.x

3. Hesdorffer DC, Benn EK, Cascino GD, Hauser WA. Is a first acute symptomatic seizure epilepsy? Mortality and risk for recurrent seizure. *Epilepsia.* (2009) 50:1102–8. doi: 10.1111/j.1528-1167.2008.01945.x

4. Lin R, Yu Y, Wang Y, Foster E, Kwan P, Lin M, et al. Risk of Post-stroke epilepsy following stroke-associated acute symptomatic seizures. *Front Aging Neurosci.* (2021) 13:707732. doi: 10.3389/fnagi.2021.707732

5. Hauser WA, Beghi E. First seizure definitions and worldwide incidence and mortality. *Epilepsia.* (2008) 49(Suppl. 1):8–12. doi: 10.1111/j.1528-1167.2008.01443.x

6. Hesdorffer DC, Logroscino G, Cascino G, Annegers JF, Hauser WA. Risk of unprovoked seizure after acute symptomatic seizure: effect of status epilepticus. *Ann Neurol.* (1998) 44:908–12. doi: 10.1002/ana.410440609

7. Galovic M, Döhler N, Erdélyi-Canavese B, Felbecker A, Siebel P, Conrad J, et al. Prediction of late seizures after ischaemic stroke with a novel prognostic model (the SeLECT score): a multivariable prediction model development and validation study. *Lancet Neurol.* (2018) 17:143–52. doi: 10.1016/S1474-4422(17)30404-0

8. Wang X-P, Zhong J, Lei T, Wang H-J, Zhu L-N, Chu S, et al. Development and external validation of a predictive nomogram model of posttraumatic epilepsy: a retrospective analysis. *Seizure.* (2021) 88:36–44. doi: 10.1016/j.seizure.2021.03.023

9. Hauser WA, Lee JR. Do seizures beget seizures? *Prog Brain Res.* (2002) 135:215–9. doi: 10.1016/S0079-6123(02)35021-0

10. Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE official report: a practical clinical definition of epilepsy. *Epilepsia.* (2014) 55:475–82. doi: 10.1111/epi.12550

11. Hauser WA, Rich SS, Lee JR, Annegers JF, Anderson VE. Risk of recurrent seizures after two unprovoked seizures. *N Engl J Med.* (1998) 338:429–34. doi: 10.1056/NEJM199802123380704

12. Claassen J, Mayer SA, Kowalski RG, Emerson RG, Hirsch LJ. Detection of electrographic seizures with continuous EEG monitoring in critically ill patients. *Neurology.* (2004) 62:1743–8. doi: 10.1212/01.WNL.0000125184.88797.62

13. Claassen J, Jetté N, Chum F, Green R, Schmidt M, Choi H, et al. Electrographic seizures and periodic discharges after intracerebral hemorrhage. *Neurology.* (2007) 69:1356–65. doi: 10.1212/01.wnl.0000281664.02615.6c

14. Bentes C, Martins H, Peralta AR, Morgado C, Casimiro C, Franco AC, et al. Early EEG predicts poststroke epilepsy. *Epilepsia Open.* (2018) 3:203–12. doi: 10.1002/epi4.12103

15. Rodriguez Ruiz A, Vlachy J, Lee JW, Gilmore EJ, Ayer T, Haider HA, et al. Association of periodic and rhythmic electroencephalographic patterns with seizures in critically ill patients. *JAMA Neurol.* (2016) 74:181–8. doi: 10.1001/jamaneurol.2016.4990

16. Punia V, Bena J, Krishnan B, Newey C, Hantus S. New onset epilepsy among patients with periodic discharges on continuous electroencephalographic monitoring. *Epilepsia.* (2018) 59:1612–20. doi: 10.1111/epi.14509

17. Punia V, Fitzgerald Z, Zhang X, Huynh H, Bena J, Morrison S, et al. Electroencephalographic biomarkers of epilepsy development in patients with acute brain injury: a matched, parallel cohort study. *Ann Clin Transl Neurol.* (2019) 6:2230–9. doi: 10.1002/acn3.50925

18. Punia V, Ellison L, Bena J, Chandan P, Sivaraju A, George P, et al. Acute epileptiform abnormalities are the primary predictors of post-stroke epilepsy: a matched, case-control study. *Ann Clin Transl Neurol.* (2022) 9:558–63. doi: 10.1002/acn3.51534

19. Hesdorffer DC, D'Amelio M. Mortality in the first 30 days following incident acute symptomatic seizures. *Epilepsia.* (2005) 46(Suppl. 1):43–5. doi: 10.1111/j.1528-1167.2005.00408.x

20. Carney N, Totten AM, O'Reilly C, Ullman JS, Hawryluk GWJ, Bell MJ, et al. Guidelines for the management of severe traumatic brain injury, fourth edition. *Neurosurgery.* (2017) 80:6–15. doi: 10.1227/NEU.0000000000001432

21. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke. *Stroke.* (2019) 50:e344–418. doi: 10.1161/STR.0000000000000211

22. Greenberg SM, Ziai WC, Cordonnier C, Dowlatshahi D, Francis B, Goldstein JN, et al. 2022 Guideline for the management of patients with spontaneous intracerebral hemorrhage: a guideline from the American Heart Association/American Stroke Association. *Stroke.* (2022) 53:e282–361. doi: 10.1161/STR.0000000000000407

23. Holtkamp M, Beghi E, Benninger F, Kälviäinen R, Rocamora R, Christensen H. European stroke organisation guidelines for the management of post-stroke seizures and epilepsy. *Eur Stroke J.* (2017) 2:103–15. doi: 10.1177/2396987317705536

24. Pandey S, Rathore C, Michael BD. Antiepileptic drugs for the primary and secondary prevention of seizures in viral encephalitis. *Cochrane database Syst Rev.* (2016) 2016:CD010247. doi: 10.1002/14651858.CD010247.pub3

25. Alvarez V, Rodriguez Ruiz AA, LaRoche S, Hirsch LJ, Parres C, Voinescu PE, et al. The use and yield of continuous EEG in critically ill patients: a comparative study of three centers. *Clin Neurophysiol.* (2017) 128:570–8. doi: 10.1016/j.clinph.2017.01.001

26. Kilbride RD, Costello DJ, Chiappa KH. How seizure detection by continuous electroencephalographic monitoring affects the prescribing of antiepileptic medications. *Arch Neurol.* (2009) 66:723–8. doi: 10.1001/archneurol.2009.100

27. Punia V, Honomichl R, Chandan P, Ellison L, Thompson N, Sivaraju A, et al. Long-term continuation of anti-seizure medications after acute stroke. *Ann Clin Transl Neurol.* (2021) 8:1857–66. doi: 10.1002/acn3.51440

28. Glass HC, Soul JS, Chang T, Wusthoff CJ, Chu CJ, Massey SL, et al. Safety of early discontinuation of antiseizure medication after acute symptomatic neonatal seizures. *JAMA Neurol.* (2021) 78:817–25. doi: 10.1001/jamaneurol.2021.1437

29. Punia V, Garcia CG, Hantus S. Incidence of recurrent seizures following hospital discharge in patients with LPDs (PLEDs) and nonconvulsive seizures recorded on continuous EEG in the critical care setting. *Epilepsy Behav.* (2015) 49:250–4. doi: 10.1016/j.yebeh.2015.06.026

30. Byrnes M, Chandan P, Newey C, Hantus S, Punia V. Acute symptomatic seizure associated with chronic antiseizure medication use after stroke. *Neurol Clin Pract.* (2022) 12:e154–61. doi: 10.1212/CPJ.0000000000200085

31. Ching DJ, Hirsch LJ. Which EEG patterns warrant treatment in the critically ill? Reviewing the evidence for treatment of periodic epileptiform discharges and related patterns. *J Clin Neurophysiol.* (2005) 22:79–91 doi: 10.1097/01.WNP.0000158699.78529.AF

32. Leung T, Leung H, Soo YOY, Mok VCT, Wong KS. The prognosis of acute symptomatic seizures after ischaemic stroke. *J Neurol Neurosurg Psychiatry.* (2017) 88:86–94. doi: 10.1136/jnnp-2015-311849