

“Special Issue on Epilepsy & Comorbidities”

Epilepsy and comorbidities: towards unravelling the common underlying mechanisms

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Epilepsy is a chronic neurological disorder characterized by the rapid occurrence of epileptic seizures affecting approximately 70 million people worldwide [1,2]. The quality of life of people with epilepsy (PWE) is challenged by a series of comorbidities that might include neurologic and neuropsychiatric disorders (cognitive decline, depression, anxiety, schizophrenia, and autism) as well as metabolic, cardiovascular and respiratory diseases [3]. Neurobehavioral and other comorbidities might share a reciprocal and complex relationship with epileptogenesis and ictogenesis thus biomarkers of the former might be useful for the prediction of the latter and vice versa [4]. This bidirectional relationship between epilepsy and associated comorbidities has attracted significant attention in recent years as supported by data showing that one half of PWE demonstrate cognitive impairments [5], 30-50%

depressive behavior, 10-25% anxiety disorders [6] and 5-40% autism or autism spectrum disorder (ASD) [7]. In the past decades, epilepsy-related neurobehavioral comorbidities have been critically discussed, but the current need in unraveling the precise mechanism associated with epilepsy and these neurobehavioral comorbidities is unmet. The precise understanding of the mechanistic pathway underlying these epilepsy-associated comorbid conditions could be instrumental in developing therapeutic interventions that might modify seizure burden and accompanying comorbid conditions.

Much more remained to be learned about the pathophysiology of epileptogenesis [8], but accumulating evidences suggest that inflammatory cascades might play a crucial role in epileptogenesis [9,10]. The role of inflammation in epilepsy is well-

documented in the literature and ample of evidence suggest that the same inflammatory pathways might be associated with other comorbid conditions such as cognitive dysfunction [11,12], depression [13,14], ASD [15], anxiety [16] and schizophrenia [17]. But there might be other mechanisms that have been implicated in various epilepsy-related comorbid conditions. For instance, indoleamine 2, 3-dioxygenase (IDO) plays a role in epilepsy-associated depression, as supported by findings reporting that activation of brain IDO contributes to epilepsy-induced depressive-like behavior [18]. Imbalance in neurotransmitters (NT) levels such as norepinephrine, dopamine, and serotonin, γ -aminobutyric acid (GABA) as well as neuroendocrine substances such as adrenocorticotrophic hormone, and neuropeptide Y (NPY) have been hypothesized to play a role in the pathogenesis of anxiety-like behavior in epilepsy [19,20]. ASD and epilepsy are hypothesized to be associated with disruption in γ -aminobutyric acid (GABA) neurotransmission affecting the excitation-inhibition signaling balance [21]. Whenever there is a disruption in molecular cascades involved in neuronal development, synaptogenesis, interneuronal function, enhanced protein synthesis in the mammalian target of rapamycin (mTOR) pathways, GABA and glutamate NMDA receptor function, as well as abnormalities in Na⁺ channel, this disruption might cause both epilepsy and ASD [22]. Moreover, changes in GABAergic activity and some genes, which code for GABAergic receptors and neurexins have been correlated to epilepsy and ASD. Moreover, a product of gene 'SYNGAP' also play an important role for neurotransmission. However, The interplay between genetics, epilepsy, and its comorbidities should not be ruled out [23]. A recent review had shed light on the role of inflammation in epilepsy and related neurobehavioral comorbidities as well as highlighted that anti-inflammatory therapy might be a candidate intervention that might modify iktogenesis and ameliorate associated neurobehavioral conditions [15,24]. However, the important question remains unsolved; is inflammation the only underlying mechanism between epilepsy and related comorbidities? This finding does not completely solve

the crucial problem, as there might be other mechanisms associated with epilepsy and related comorbid conditions that are not yet explored. Moreover, no experimental and clinical evidence has further substantiated these findings warranting further research in this domain.

Epilepsy and related comorbid conditions, as well as the plausible interplay mechanism, constitutes a novel research arena that deserves to be extensively studied. The scope of this topic is not only limited to unraveling the mechanism associated with epilepsy and related comorbidities, but also extends towards developing suitable animal models for investigating epilepsy and comorbidities as well as identifying potential new biomarkers that would allow for the prediction, diagnosis, and treatment of epilepsy-related comorbidities [4]. This research topic is of crucial importance as the complex association between epilepsy and comorbid conditions exhibits a greater difficulty in epilepsy treatment and might hinder the outcome of the therapy. The more complicating issues reside in the fact that, epilepsy is not only a single disorder but is a broad range of systemic disorders with shared and common features [8]. Though this research topic will strengthen the state of knowledge of the comorbidities associated with epilepsy, the research in this domain is completely challenging yet interesting. The treatment process of PWE is full of complexity since the main concern still remained unsolved; do these comorbidities associated with epilepsy persist even after epilepsy is resolved?

On top of that, the current research topic will encourage new research avenues and opportunities for further improvement in clinical care and scientific discovery. The research on epilepsy and related comorbidities is utterly crucial and is a current need as the better understanding of the precise mechanisms of comorbidities could help to prevent morbidity and premature mortality of PWE. We are confident that this special issue will provide novel and insightful information to the readers that would spark new research in the field of epilepsy.

References

1. Paudel YN, Shaikh MF, Chakraborti A, Kumari Y, Aledo-Serrano Á, Aleksovska K, et al. HMGB1: A Common Biomarker and Potential Target for TBI, Neuroinflammation, Epilepsy, and Cognitive Dysfunction. *Frontiers in Neuroscience*. 2018;12:628. <https://doi.org/10.3389/fnins.2018.00628>
2. Josephson CB, Jetté N. Psychiatric comorbidities in epilepsy. *Int Rev Psychiatry*. 2017;29(5):409-424. <https://doi.org/10.1080/09540261.2017.1302412>
3. Gaitatzis A, Sisodiya SM, Sander JW. The somatic comorbidity of epilepsy: A weighty but often unrecognized burden. *Epilepsia*. 2012;53(8):1282-1293. <https://doi.org/10.1111/j.1528-1167.2012.03528.x>
4. Ravizza T, Onat FY, Brooks-Kayal AR, Depaulis A, Galanopoulou AS, Mazarati A, et al. WONOEP appraisal: Biomarkers of epilepsy-associated comorbidities. *Epilepsia*. 2016;58(3):331-342. <https://doi.org/10.1111/epi.13652>
5. Allendorfer JB, Arida RM. Role of Physical Activity and Exercise in Alleviating Cognitive Impairment in People With Epilepsy. *Clinical Therapeutics*. 2018;40(1):26-34. <https://doi.org/10.1016/j.clinthera.2017.12.004>
6. Lopez-Gomez M, Espinola M, Ramirez-Bermudez J, Sosa AL. Clinical presentation of anxiety among patients with epilepsy. *Neuropsychiatric Disease and Treatment*. 2008;4(6):1235-1239. <https://doi.org/10.2147/ndt.s3990>
7. Kohane IS, McMurry A, Weber G, MacFadden D, Rappaport L, Kunkel L, et al. The co-morbidity burden of children and young adults with autism spectrum disorders. *PLoS ONE*. 2012;7(4):e33224. <https://doi.org/10.1371/journal.pone.0033224>
8. Keezer MR, Sander JW. Epilepsy is a neurological and a systemic disorder. *Epilepsy & Behavior*. 2018;78:57-61. <https://doi.org/10.1016/j.yebeh.2017.10.010>
9. Vezzani A. Inflammation and Epilepsy. *Epilepsy Currents*. 2005;5(1):1-6. <https://doi.org/10.1111/j.1535-7597.2005.05101.x>
10. Vezzani A, French J, Bartfai T, Baram TZ. The role of inflammation in epilepsy. *Nature Reviews Neurology*. 2010;7(1):31-40. <https://doi.org/10.1038/nrneuro.2010.178>
11. Marsland AL, Gianaros PJ, Sheu LK, Krajina K, Manuck SB. Brain morphology links systemic inflammation to cognitive function in midlife adults. *Brain, Behavior, and Immunity*. 2015;48:195-204. <https://doi.org/10.1016/j.bbi.2015.03.015>
12. McAfoose J, Baune BT. Evidence for a cytokine model of cognitive function. *Neurosci Biobehav Rev*. 2008;33(3):355-366. <https://doi.org/10.1016/j.neubiorev.2008.10.005>
13. Slavich GM, Irwin MR. From stress to inflammation and major depressive disorder: A social signal transduction theory of depression. *Psychological Bulletin*. 2014;140(3):774-815. <https://doi.org/10.1037/a0035302>
14. Krishnadas R, Cavanagh J. Depression: an inflammatory illness? *J Neurol Neurosurg Psychiatry*. 2012;83(5):495-502. <https://doi.org/10.1136/jnnp-2011-301779>
15. Mazarati AM, Lewis ML, Pittman QJ. Neurobehavioral comorbidities of epilepsy: Role of inflammation. *Epilepsia*. 2017;58(Suppl 3):48-56. <https://doi.org/10.1111/epi.13786>
16. Vogelzangs N, Beekman ATF, de Jonge P, Penninx BWJH. Anxiety disorders and inflammation in a large adult cohort. *Translational Psychiatry*. 2013;3(4):e249. <https://doi.org/10.1038/tp.2013.27>
17. Müller N, Weidinger E, Leitner B, Schwarz MJ. The role of inflammation in schizophrenia. *Frontiers in Neuroscience*. 2015;9:372. <https://doi.org/10.3389/fnins.2015.00372>
18. Xie W, Cai L, Yu Y, Gao L, Xiao L, He Q, et al. Activation of brain indoleamine 2,3-dioxygenase contributes to epilepsy-associated depressive-like behavior in rats with chronic temporal lobe epilepsy. *J Neuroinflammation*. 2014;11(1):41. <https://doi.org/10.1186/1742-2094-11-41>
19. Depaulis A, Helfer V, Deransart C, Marescaux C. Anxiogenic-like consequences in animal models of complex partial seizures. *Neurosci Biobehav Rev*. 1998;21(6):767-774. [https://doi.org/10.1016/S0149-7634\(96\)00060-7](https://doi.org/10.1016/S0149-7634(96)00060-7)
20. Vazquez B, Devinsky O. Epilepsy and anxiety. *Epilepsy Behav*. 2003;4 Suppl 4:S20-25. <https://doi.org/10.1016/j.yebeh.2003.10.005>

21. Frye RE, Casanova MF, Fatemi SH, Folsom TD, Reutiman TJ, Brown GL, et al. Neuropathological Mechanisms of Seizures in Autism Spectrum Disorder. *Frontiers in Neuroscience*. 2016;10:192. <https://doi.org/10.3389/fnins.2016.00192>
22. Richard AE, Scheffer IE, Wilson SJ. Features of the broader autism phenotype in people with epilepsy support shared mechanisms between epilepsy and autism spectrum disorder. *Neurosci Biobehav Rev*. 2017;75:203-233. <https://doi.org/10.1016/j.neubiorev.2016.12.036>
23. Keezer MR, Sisodiya SM, Sander JW. Comorbidities of epilepsy: current concepts and future perspectives. *The Lancet Neurology*. 2016;15(1):106-115. [https://doi.org/10.1016/s1474-4422\(15\)00225-2](https://doi.org/10.1016/s1474-4422(15)00225-2)
24. Paudel YN, Shaikh MF, Shah S, Kumari Y, Othman I. Role of inflammation in epilepsy and neurobehavioral comorbidities: Implication for therapy. *Eur J Pharmacol*. 2018;837:145-155. <https://doi.org/10.1016/j.ejphar.2018.08.020>