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REVIEW ARTICLE

The Progress of Epilepsy after Stroke

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Abstract: ***Background*:** Epilepsy is the second most common disease caused by multiple factors and characterized by an excessive discharge of certain neurons in the nervous system. Cerebrovascular disease, including stroke, is viewed as the most common cause of epilepsy in the elderly population, accounting for 30%-50% of the newly diagnosed cases of epilepsy cases in this age group.

***Methods*:** Data were collected from Web of Science, Medline, Pubmed, Scopus, through searching of these keywords: "Stroke" and "epilepsy".

***Results*:** Depending on the underlying cerebrovascular disease, 3%-30% of patients after stroke may develop post-stroke epilepsy (PSE), which has a negative effect on stroke prognosis and the quality of life.

***Conclusion*:** In this review, we summarized new aspects emerging from research into PSE, including definition, epidemiology, risk factors, mechanism, accessory examination and treatment strategies for post-stroke epilepsy, which will enrich our knowledge of this disorder.

Keywords: Epilepsy, stroke, seizure, post-stroke epilepsy, risk factor, brain.

1. INTRODUCTION

Epilepsy is the second most common disease caused by multiple factors and characterized by an excessive discharge of certain neurons in the nervous system [1]. According to an epidemiological survey, epilepsy affects approximately 0.5% of the human population [2].

Stroke is a serious global public health problem and a leading cause of death and disability [3]. Cerebrovascular diseases, including stroke, are viewed as the most common cause of epilepsy in the elderly population, accounting for 30%-50% of the newly diagnosed cases of epilepsy cases in this age group [4-6]. A large number of epidemiological studies have suggested that large artery atherosclerosis (LAD), cardioembolism (CE), small vessel disease (SVD) [7-9] and others such as inflammatory disease [10], hyper coagulable states [11], and arterial dissection [12] in adults may contribute to the development of stroke. In stroke, seizures occur in the very acute state and years after the stroke in patients with large hematomas and infarcts, as well as subtle structural abnormalities of the brain [13, 14]. Several studies in experimental models and human have reported that the changes after stroke, including critically decreased regional blood flow, a low regional cerebral metabolic rate for oxygen and increased blood-brain barrier permeability made the brain prone to seizures [15-17]. Seizures following stroke are usually divided into early or late onset according to an arbitrary cut point of 2 weeks after the presenting stroke. Approximately 5-10% of patients after stroke present early onset seizures with the first 2 weeks [18-20] and also manifest late onset seizures with more than 2 weeks after the stroke [21, 22]. The occurrence of a late seizure is required for the diagnosis of post-stroke epilepsy (PSE). Depending on the underlying cerebrovascular disease, 3%-30% of patients after stroke may develop PSE, which has a negative effect on stroke prognosis and the quality of life [23-26]. In this review, we will describe new aspects emerging from research into PSE, including definition, epidemiology, risk factors, mechanism, accessory examination and treatment strategies for post-stroke epilepsy.

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2. DEFINITION

Post-stroke seizures (PSS) have been classified as occurring immediately before, immediately after (24 hours), or of early or late onset. Early-onset seizures are considered to be provoked seizures, which occurred within 1 week [27-29] or 2 weeks [14, 18] after stroke and caused by the acute metabolic and physiological derangement associated with acute infarction. Late-onset seizures after 2 weeks of stroke are considered to be unprovoked seizures that originate from the areas of partially injured brain where neuronal networks have undergone anatomical and physiological alterations, predisposing them to hyperexcitability and synchronization [30, 31]. PSE was defined as 2 or more unprovoked late-onset epileptic seizures following stroke with confirmed diagnosis of epilepsy that occurred after the acute phase of the stroke and in the absence of other obvious causes or a history of prestroke epilepsy [14, 25, 32].

3. EPIDEMIOLOGY

The incidence of epilepsy after stroke in elderly varies widely, from 2% to 33% for early seizures [19, 20, 28, 33, 34], 3% to 4.5% for late seizures [21, 22], and 2% to 4% for PSE [25, 35, 36]. Sazflarski *et al.* found that the overall incidence of acute seizures within the first 24 hours of stroke was 3.1% [37]. Mohamed *et al.* reported that early seizures occurred in about 13% of patient with acute stroke, in whom hemorrhagic transformation is a predictive factor for early seizures [20]. Kammersfaard *et al.* reported that PSE occurred in about 3% of all patients with stroke within 7 years after stroke [38]. One meta-analysis showed that seizures occurred in about 6.93% of people with stroke [39]. This variation in the incidence of early seizures, late seizures and PSE reflects the differences in the patient populations, definition of the term for PSE, study design, diagnostic criteria, and the duration of follow-up [25, 35, 40, 41]. Recently, higher figures for PSE have generally been found, but it is not possible to identify a clear temporal trend with any certainty, due to methodological differences.

4. RISK FACTORS

It is very difficult to predict who is likely to develop epilepsy after the stroke. However, many studies described different risk factors associated with a higher incidence of PSE such as stroke subtypes, cortical involvement, large infarction, stroke severity, acute confusional state and vascular risk factor [23, 26, 42-45]. The risk factors for acute symptomatic seizure and late post-stroke seizure in young ischaemic stroke were different to older ischemic stroke patients [46]. Strzelczyk *et al*. reported that post-stroke epilepsy risk scale (PoSERS) was a valuable tool to predict the risk for PSE within the first few days after stroke [47].

4.1. Stroke Subtypes

Stroke can be classified into two major categories: ischemic and hemorrhagic strokes [48]. PES occurred more commonly with hemorrhagic stroke than with ischemic stroke (IS), with about 10-20% of patients developing PSE after hemorrhagic stroke compared with 2-14% after ischemic stroke [23, 38, 41, 49]. Christopher F *et al.* reported that patients with hemorrhagic stroke were at a significantly greater risk of seizures with an almost 2-fold increase risk of seizure after stroke in 1897 patients with acute stroke [18]. Sazflarski *et al.* reported that the incidence of seizures in patients with ischemic stroke was 2.4% while the incidence of seizures in patients with hemorrhagic stroke was significantly higher (8.4%) [37]. Krakow *et al.* analyzed 58,874 patients with acute post-stroke (aPSS) seizures in Germany and found PSE occurred in 0.7% of patient with transient ischemic attack (TIA), in 2.2% of patients with ischemic stroke and in 5.1% of patients with intracerebral hemorrhage (ICH) [50].

4.2. Stroke Severity

Clinical stroke severity is a major factor in the development of PSE [18, 24-26, 51]. Graham *et al.* reported that low Glasgow Coma Scale (GCS) score, incontinence, dysarthria or poor function on Barthel Index as a measure of stroke severity were associated with PSE, which are suggestive of an association of PSE with more severe stroke [25].

4.3. Lesion Locations

Extent of cortical involvement is a significant risk factor for early post-stroke seizures [18, 34, 52]. Post-stroke seizures were more likely to develop in patients with larger lesions involving multiple lobes of the brain than in those with single lobar involvement [44]. Patients with recurrent post-stroke seizures were more likely to have a cortical lesion, especially in the frontal lobe [53, 54]. Zou *et al.* found that post-stroke seizures occurred more commonly after hemorrhagic stroke and when stroke occurred in the cortical region [39]. However, Szaflarski *et al.* found that localization of the ischemic stroke did not influence the risk for seizure development [37]. Some evidence suggests that post-stroke epilepsy also varies depending on the affected cortical area. Involvement of the parieto-temporal cortex, supramarginal gyrus, and superior temporal gyrus seems to be associated with post-stroke epileptogenesis [18, 55-57].

4.4. Vascular Risk Factors

A large study in the UK reported that vascular risk factors including history of myocardial infarction, peripheral vascular disease, hypertension, total serum cholesterol, and left ventricular hypertrophy, are associated with late-onset epilepsy [58], which are supported by a meta-analysis published in 2014 [59]. Benbir G *et al.* found that Lacunar infarctions form about 11% of post-ischemic epilepsy, which are often discussed in the context of leukoaraiosis [60]. Gasparini *et al.* studied patients with epilepsy with leukoaraiosis frequently clinical and EEG signs suggestive of temporal lobe epilepsy, but patients with large vessel infarct had signs of frontal lobe epilepsy, corresponding with a cortical or central localization of the infarct [61]. Furthermore, patients with leukoaraiosis and lacunoarinfarct with impaired cognition had a greater risk for PSE than patients with cognitive impairment [62]. Conrad *et al.* reported that epileptic seizures occurred in particular after major strokes and in sinus thrombosis [63]. Interestingly, conventional vascular risk factors including transient ischemic attack (TIA), different types of bleeding and intracranial venous thrombosis (IVT)

were not associated with the occurrence of post-stroke seizures [63].

4.5. Genetic Factors

About 30% of all epilepsy syndromes are believed to be of genetic origin and more than 500 loci are associated with epilepsy in human beings and mice [64]. Yang *et al.* reported that the *ALDH2* (aldehyde dehydrogenase 2) *rs671* polymorphism was associated with PSE and increased the plasma concentration of ALDH2 substrate, 4-hydrozynonenal (4-HNE) levels [65]. Zhang *et al.* reported that a *CD40-1C/T* polymorphism was associated with PSE susceptibility through raising plasma concentrations of sCD40L, which is involved in the inflammatory response [66, 67]. Transcriptomic profiling showed that a functional connectivity seemed to exist between many of the genes that modulate post-ischemic stroke outcomes [45]. Now no studies showed that a given polymorphism could increase the association of PSE with a specific comorbidity.

4.6. Others

Wallace *et al*. reported that both age specific incidence and prevalence of epilepsy are higher in older people [58, 68] and also found that the prevalence of epilepsy is as high as nearly 1% in people 85 years and over [68]. In Chadehumbe's large population-based cohort, seizures occurred within 24 hours of the stroke in 58% of children. The authors found that seizures were 18 times more likely in children than adults within 24 hours of noted stroke symptoms within the acute setting of children stroke being common [69]. Moreover, Suppiej *et al.* investigated the risk of pediatric epilepsy following neonatal seizures symptomatic of stroke and found that neonatal seizures symptomatic of perinatal arterial ischemic stroke had lower risk and later onset of post-neonatal epilepsy compared to seizures described in the setting of other perinatal brain insults [70]. In addition, Hauser *et al.* found that the risk of the seizure at older ages was higher for men as compared to women [71].

5. MECHANISM

5.1. The Epilepsy after Ischemic Stroke

Various patho-physiological mechanisms underlying early seizures, late seizures and PSE with a predominance of acute cellular biochemical disturbances have been proposed. Neurotransmitter amino acids play an important role in the pathogenesis and development of epilepsy [72]. Increased concentration of the excitatory neurotransmitter glutamate (Glu), the disturbance of electrolyte balance, the destruction of phospholipid membranes, and the secretion of free fatty acids have been documented in the penumbral areas in the acute post-ischemic stroke phase [73-76]. Sun *et al.* found that glutamate injury produced a permanent epileptiform phenotype after stroke in a novel *in vitro* model [75]. Two studies reported that the inhibitory networks in the perilesional cortex with photo thrombotic infarcts, including changes in the staining intensity of neuropeptide Y neurons and GABA receptor subunits, remain certain for the contribution to post-stroke epileptogenesis [77, 78]. Interestingly, hyper-susceptibility to pentylenetetrazole (PTZ, a GABA antagonist) induced seizure following brain hypoxia/ischemia was mediated by the interaction of opioidergic, and iNOS/NO (nitric oxide) pathways [79]. Seizures may exacerbate secondary injury by inducing glutamate excitotoxicity and/or enhancing the mismatch between energy supply and demand under ischemic conditions, leading to breakdown of ion gradients, mitochondrial damage, and eventually an irreversible state of injury [23]. Repeated seizure-like activity in the setting of cerebral ischemia significantly increases infarct size and can impair functional recovery, an effect that can be ameliorate with the administration of certain neuroprotective agents [80]. Calcium ion accumulation in hippocampal neurons has been known as a major contributor to the etiology of epilepsy. TRPV1 is a calcium-permeable channel and mediator of epilepsy in the hippocampus and its activation induced epileptic effects, which may possibly be a novel target for the prevention of epileptic seizures [81]. In addition, the accumulation of intracellular calcium and sodium resulted in depolarization of the transmembrane potential and activation of Ca^{2+} downstream signaling pathways, as well as shifts in ionic potential, which could be blocked by Ca^{2+} channel blocker through lowering the seizure threshold [82, 83].

5.2. The Epilepsy after Hemorrhagic Stroke

The factors provoking seizures following intracerebral hemorrhage are related to hemorrhage volume, hemorrhage location within the cerebrum, cortical involvement and the severity of neurological deficits [22, 84, 85]. Systemic administration of sodium salicylate (NaSal) leads to hemorrhage, cell death and proliferation of microglia in rats with Kainic acid (KA)-induced seizures. Importantly, the hemorrhage was restricted to the areas of the brain where KA is known to elicit seizure activity, which suggests that the induction of seizure is a necessary requirement for NaSal to cause hemorrhage [86]. In addition, Jo *et al.* developed an animal model of chronic epilepsy using nanoscale iron injection into the adult mouse cortex, which mimics some aspects of microhemorrhagic brain injury, were correlated with the degree of reduction in the number of GABAergic interneurons [87]. In fact, epilepsy after hemorrhagic stroke is thought to be attributable to irritation casued by products of blood metabolism. The exact pathophysiology is unclear, but an associated ischemic area secondary to hemorrhage may play a part in the epilepsy after hemorrhagic stroke.

6. ACCESSORY EXAMINATION

Electroencephalogram (EEG) is the most frequent neurodiagnostic method for detecting epileptic activity, especially in patients with non-convulsive post-stroke epileptic activity [13]. Patients who had EEG showing periodic lateralized and bilateral independent periodic lateralized epileptiform discharges were prone to a higher risk of post-stroke seizures development. EEG may help to detect specific patterns, such as Periodic Lateralized Epileptiform Discharges (PLEDs) that are closely related to early seizures [88-90]. But the sensitivity and specificity of epileptiform changes in EEG were poor and showed little value to predict the progression to status epileptics. To further determine stroke types, all patients underwent brain imaging with computed tomography

(CT), magnetic resonance imaging (MRI) or both. When cerebral perfusion-CT (PCT) abnormalities occurred in atypical vascular distributions and the CT Angiography (CTA) showed no corresponding large vessel occlusions, which could be as a diagnostic possibility prior to giving acute stroke therapy [91]. Koome *et al.* reported that Computed Tomography Perfusion (CTP) might improve sensitivity and specificity of cortical involvement for post-stroke seizure compared to non-contrast CT (NCCT) [92]. An increase in lesion size on CT in patients with delayed seizures and epilepsy after ischemic stroke showed a trend of more severe disability [93]. In addition, SPECT-DTPA was a tool for evaluating the disruption of blood-brain barrier to predict developing seizures in patients with cortical stroke [94]. Recently, Arterial spin-labeling (ASL), a non-contrast-enhanced sequence of magnetic resonance imaging (MRI) has been reported as useful in early seizure [95] and in the differentiation of late seizure [96] due to simultaneous evaluation of changes to both cerebral perfusion and the primary stroke lesion.

7. TREATMENT

7.1. Drugs

Due to different mechanisms of PSE, there are different treatments and outcomes between early seizures and late seizures. At one extreme, status epileptics required urgent intravenous therapy and at the other an isolated short-lived seizure in the early phase may require no specific therapy [23]. De Reuck's study while specifically analyzing the risk factors for developing epilepsy found that early seizures did not require long-term anti epileptic therapy to prevent recurrence, in contrast to late-onset seizures [97]. Although stroke is a major cause of epilepsy, no published guidelines specifically address the treatment of PSE [98]. Currently, numerous antiepileptic drugs (AEDs) are approved for controlling epilepsy with different etiologies, but studies on managing post-stroke epilepsy have offered conflicting results. Expert opinion in adults in the USA published by Karceski *et al.* rated lamotrigine (LTG) as the treatment of choice in either medically stable or ill elderly patients [99]. A large nationwide, population-based study demonstrated that late-onset PSE patients using valproic acid (VPA) and new AEDs have better seizure control than those using phenytoin (PHT) as demonstrated by lower risks of emergency room visits and hospitalization [100]. A pilot study suggested that intravenously administered lacosamide (LCM) exhibited safety and efficacy profiles, which make it an optimal candidate as a first-choice drug against post-stroke non-convulsive status epilepticus (NCSE) in elderly patients [101]. Shetty *et al.* reported that levetiracetam (LEV) treatment had promise for restraining status epilepticus and stroke-induced chronic epilepsy [102]. *In vitro* and *in vivo* studies showed that gap junctions are clusters of intercellular channels allowing the bidirectional pass of ions directly into the cytoplasm of adjacent cells and were blocked by compounds with anticonvulsant effects to modify the behavioral parameters related to seizures, which could provide a promising avenue for the treatment of epilepsy [103]. However, a study by Neshige and colleagues showed that AEDs therapy had poor association with preventing the recurrence of post-stroke seizures [84].

Oxidative stress is believed to directly participate in many pathways leading to an enduring predisposition to generate epileptic seizures, which serves as the most important propagating factor for declining the epileptic condition. Various antioxidants showed numerous beneficial effects on oxidative stress markers and neuroprotective effects in animal seizure models. However, till now only a few antioxidants have been further applied to patients with epilepsy as an add-on therapy [104].

7.2. Invasive Interventions

Surgical intervention for the management of the epilepsy in patients after strokes could improve the quality and expectancy of life. Laser ablation is an effective treatment strategy for medically refractory post-stroke epilepsy [105]. In children, periinsular hemispherotomy was considered an alternative in the therapeutic approach to stroke-induced pediatric refractory epilepsy [106]. Moreover, Ghatan *et al.* reported that epilepsy surgery was effective in controlling medically intractable seizures after perinatal vascular insults with significant improvements in independence, quality of life, cognitive development, and motor skills [107].

Overall, the general principles of management used for epilepsy are applied to the management of post-stroke seizures and post-stroke epilepsy. The treatment for post-stroke epilepsy elicited and controlled seizures by drugs or surgical treatment in order to improve quality of life, cognitive development, and motor skills. However, the main limitations for all AEDs revolved around an associated sedation and the possibility of drug interaction increased the chance of toxic effects in older population. Surgical treatments of intractable epilepsy had been considered a valuable means of controlling seizures, but less considered as potential therapeutic intervention.

CONCLUSION

In 2014, the Working Group of the International League against Epilepsy revised the terminology related to the term epileptogenesis. The task force proposed that epilepsy is considered to be a disease of the brain defined by any of the following conditions: (1) At least two unprovoked (or reflex) seizures occurring >24 hours apart; (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; (3) diagnosis of an epilepsy syndrome. The new definition takes into account evidence from preclinical studies showing that epileptogenic neurobiological processes can continue even after the appearance of spontaneous recurrent seizures. Although more focus has been laid on PSE, our understanding about etiology, possible risk factors, mechanism and clinical treatment, remains to be further explored. According the new definition of PSE, the epidemiology will have a great change. However, closed-loop, ontogenetic technologies will shed more light on our researches about the diagnosis and treatment of PSE.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Liu, W.; Ge, T.; Pan, Z.; Leng, Y.; Lv. J.; Li, B. The effects of herbal medicine on epilepsy. *Oncotarget*, **2017**, *8*(29), 48385-48397.

[2] Leonardi, M.; Ustun, T.B. The global burden of epilepsy. *Epilepsia,* **2002**, *43*(Suppl. 6), 21-25. [http://dx.doi.org/10.1046/j.1528-1157.43.s.6.11.x] [PMID: 12190974]

[3] Feigin, V.L.; Lawes, C.M.; Bennett, D.A.; Barker-Collo, S.L.; Parag, V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. *Lancet Neurol.,* **2009**, *8*(4), 355-369. [http://dx.doi.org/10.1016/S1474-4422(09)70025-0] [PMID: 19233729]

[4] Rowan, A.J. Epilepsy in older adults. Common morbidities influence development, treatment strategies, and expected outcomes. *Geriatrics,* **2005**, *60*(12), 30-32, 34. [PMID: 16343034]

[5] Acharya, J.N.; Acharya, V.J. Epilepsy in the elderly: Special considerations and challenges. *Ann. Indian Acad. Neurol.,* **2014**, *17*(Suppl. 1), S18-S26. [http://dx.doi.org/10.4103/0972-2327.128645] [PMID: 24791083]

[6] Brodie, M.J.; Kwan, P. Epilepsy in elderly people. *BMJ,* **2005**, *331*(7528), 1317-1322. [http://dx.doi.org/10.1136/bmj.331.7528.1317] [PMID: 16322020]

[7] Stróżyńska, E.; Fiszer, U.; Ryglewicz, D.; Zaborski, J. The impact of risk burden differences between men and women on the clinical course of ischemic stroke. *J. Stroke Cerebrovasc. Dis.,* **2016**, *25*(4), 843-847. [http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2015.12.015] [PMID: 26796054]

[8] Bang, O.Y.; Lee, P.H.; Joo, S.Y.; Lee, J.S.; Joo, I.S.; Huh, K. Frequency and mechanisms of stroke recurrence after cryptogenic stroke. *Ann. Neurol.,* **2003**, *54*(2), 227-234. [http://dx.doi.org/10.1002/ana.10644] [PMID: 12891675]

[9] Shin, D.H.; Lee, P.H.; Bang, O.Y. Mechanisms of recurrence in subtypes of ischemic stroke: a hospital-based follow-up study. *Arch. Neurol.,* **2005**, *62*(8), 1232-1237. [http://dx.doi.org/10.1001/archneur.62.8.1232] [PMID: 16087764]

[10] Misra, S.; Kumar, P.; Kumar, A.; Sagar, R.; Chakravarty, K.; Prasad, K. Genetic association between inflammatory genes (IL-1α, CD14, LGALS2, PSMA6) and risk of ischemic stroke: A meta-analysis. *Meta Gene,* **2016**, *8*, 21-29. [http://dx.doi.org/10.1016/j.mgene.2016.01.003] [PMID: 27014587]

[11] Levine, S.R. Hypercoagulable states and stroke: a selective review. *CNS Spectr.,* **2005**, *10*(7), 567-578. [http://dx.doi.org/10.1017/S109285290001021X] [PMID: 16155513]

[12] Schievink, W.I. Spontaneous dissection of the carotid and vertebral arteries. *N. Engl. J. Med.,* **2001**, *344*(12), 898-906. [http://dx.doi.org/10.1056/NEJM200103223441206] [PMID: 11259724]

[13] Silverman, I.E.; Restrepo, L.; Mathews, G.C. Poststroke seizures. *Arch. Neurol.,* **2002**, *59*(2), 195-201. [http://dx.doi.org/10.1001/archneur.59.2.195] [PMID: 11843689]

[14] Myint, P.K.; Staufenberg, E.F.; Sabanathan, K. Post-stroke seizure and post-stroke epilepsy. *Postgrad. Med. J.,* **2006**, *82*(971), 568-572. [http://dx.doi.org/10.1136/pgmj.2005.041426] [PMID: 16954451]

[15] Awada, A.; Omojola, M.F.; Obeid, T. Late epileptic seizures after cerebral infarction. *Acta Neurol. Scand.,* **1999**, *99*(5), 265-268. [http://dx.doi.org/10.1111/j.1600-0404.1999.tb00674.x] [PMID: 10348154]

[16] Marchi, N.; Granata, T.; Ghosh, C.; Janigro, D. Blood-brain barrier dysfunction and epilepsy: pathophysiologic role and therapeutic approaches. *Epilepsia,* **2012**, *53*(11), 1877-1886. [http://dx.doi.org/10.1111/j.1528-1167.2012.03637.x] [PMID: 22905812]

[17] van Vliet, E.A.; Aronica, E.; Gorter, J.A. Blood-brain barrier dysfunction, seizures and epilepsy. *Semin. Cell Dev. Biol.,* **2015**, *38*, 26-34. [http://dx.doi.org/10.1016/j.semcdb.2014.10.003] [PMID: 25444846]

[18] Bladin, C.F.; Alexandrov, A.V.; Bellavance, A.; Bornstein, N.; Chambers, B.; Coté, R.; Lebrun, L.; Pirisi, A.; Norris, J.W. Seizures after stroke: a prospective multicenter study. *Arch. Neurol.,* **2000**, *57*(11), 1617-1622. [http://dx.doi.org/10.1001/archneur.57.11.1617] [PMID: 11074794]

[19] Serafini, A.; Gigli, G.L.; Gregoraci, G.; Janes, F.; Cancelli, I.; Novello, S.; Valente, M. Are early seizures predictive of epilepsy after a stroke? Results of a Population-Based Study. *Neuroepidemiology,* **2015**, *45*(1), 50-58. [http://dx.doi.org/10.1159/000382078] [PMID: 26227564]

[20] Mohamed, C.; Kissani, N. Early seizures in acute stroke. *Pan Afr. Med. J.,* **2015**, *20*, 136. [http://dx.doi.org/10.11604/pamj.2015.20.136.5925] [PMID: 26097640]

[21] Okuda, S.; Takano, S.; Ueno, M.; Hamaguchi, H.; Kanda, F. Clinical features of late-onset poststroke seizures. *J. Stroke Cerebrovasc. Dis.,* **2012**, *21*(7), 583-586. [http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2011.01.006] [PMID: 21367620]

[22] Rossi, C.; De Herdt, V.; Dequatre-Ponchelle, N.; Hénon, H.; Leys, D.; Cordonnier, C. Incidence and predictors of late seizures in intracerebral hemorrhages. *Stroke,* **2013**, *44*(6), 1723-1725. [http://dx.doi.org/10.1161/STROKEAHA.111.000232] [PMID: 23640832]

[23] Menon, B.; Shorvon, S.D. Ischaemic stroke in adults and epilepsy. *Epilepsy Res.,* **2009**, *87*(1), 1-11. [http://dx.doi.org/10.1016/j.eplepsyres.2009.08.007] [PMID: 19744830]

[24] Jungehulsing, G.J.; Heuschmann, P.U.; Holtkamp, M.; Schwab, S.; Kolominsky-Rabas, P.L. Incidence and predictors of post-stroke epilepsy. *Acta Neurol. Scand.,* **2013**, *127*(6), 427-430. [http://dx.doi.org/10.1111/ane.12070] [PMID: 23398544]

[25] Graham, N.S.; Crichton, S.; Koutroumanidis, M.; Wolfe, C.D.; Rudd, A.G. Incidence and associations of poststroke epilepsy: the prospective South London Stroke Register. *Stroke,* **2013**, *44*(3), 605-611. [http://dx.doi.org/10.1161/STROKEAHA.111.000220] [PMID: 23370202]

[26] Zhang, C.; Wang, X.; Wang, Y.; Zhang, J.G.; Hu, W.; Ge, M.; Zhang, K.; Shao, X. Risk factors for post-stroke seizures: a systematic review and meta-analysis. *Epilepsy Res.,* **2014**, *108*(10), 1806-1816. [http://dx.doi.org/10.1016/j.eplepsyres.2014.09.030] [PMID: 25454500]

[27] So, E.L.; Annegers, J.F.; Hauser, W.A.; O'Brien, P.C.; Whisnant, J.P. Population-based study of seizure disorders after cerebral infarction. *Neurology,* **1996**, *46*(2), 350-355. [http://dx.doi.org/10.1212/WNL.46.2.350] [PMID: 8614493]

[28] Labovitz, D.L.; Hauser, W.A.; Sacco, R.L. Prevalence and predictors of early seizure and status epilepticus after first stroke. *Neurology,* **2001**, *57*(2), 200-206. [http://dx.doi.org/10.1212/WNL.57.2.200] [PMID: 11468303]

[29] Benbadis, S. The differential diagnosis of epilepsy: a critical review. *Epilepsy Behav.,* **2009**, *15*(1), 15-21. [http://dx.doi.org/10.1016/j.yebeh.2009.02.024] [PMID: 19236946]

[30] Kelly, K.M. Animal modeling of poststroke seizures and epilepsy: 5-year update. *Epilepsy Curr.,* **2007**, *7*(6), 159-162. [http://dx.doi.org/10.1111/j.1535-7511.2007.00211.x] [PMID: 18049725]

[31] Beghi, E.; Carpio, A.; Forsgren, L.; Hesdorffer, D.C.; Malmgren, K.; Sander, J.W.; Tomson, T.; Hauser, W.A. Recommendation for a definition of acute symptomatic seizure. *Epilepsia,* **2010**, *51*(4), 671-675. [http://dx.doi.org/10.1111/j.1528-1167.2009.02285.x] [PMID: 19732133]

[32] Kelly, K.M. Poststroke seizures and epilepsy: Clinical studies and animal models. *Epilepsy Curr.,* **2002**, *2*(6), 173-177. [http://dx.doi.org/10.1046/j.1535-7597.2002.00064.x] [PMID: 15309107]

[33] Hamidou, B.; Aboa-Eboulé, C.; Durier, J.; Jacquin, A.; Lemesle-Martin, M.; Giroud, M.; Béjot, Y. Prognostic value of early epileptic seizures on mortality and functional disability in acute stroke: the Dijon Stroke Registry (1985-2010). *J. Neurol.,* **2013**, *260*(4), 1043-1051. [http://dx.doi.org/10.1007/s00415-012-6756-3] [PMID: 23180187]

[34] Procaccianti, G.; Zaniboni, A.; Rondelli, F.; Crisci, M.; Sacquegna, T. Seizures in acute stroke: incidence, risk factors and prognosis.

Neuroepidemiology, **2012**, *39*(1), 45-50. [http://dx.doi.org/10.1159/000338374] [PMID: 22777596]

[35] Lossius, M.I.; Rønning, O.M.; Mowinckel, P.; Gjerstad, L. Incidence and predictors for post-stroke epilepsy. A prospective controlled trial. The Akershus stroke study. *Eur. J. Neurol.,* **2002**, *9*(4), 365-368. [http://dx.doi.org/10.1046/j.1468-1331.2002.00415.x] [PMID: 12099919]

[36] Chen, T.C.; Chen, Y.Y.; Cheng, P.Y.; Lai, C.H. The incidence rate of post-stroke epilepsy: a 5-year follow-up study in Taiwan. *Epilepsy Res.,* **2012**, *102*(3), 188-194. [http://dx.doi.org/10.1016/j.eplepsyres.2012.06.003] [PMID: 22749919]

[37] Szaflarski, J.P.; Rackley, A.Y.; Kleindorfer, D.O.; Khoury, J.; Woo, D.; Miller, R.; Alwell, K.; Broderick, J.P.; Kissela, B.M. Incidence of seizures in the acute phase of stroke: a population-based study. *Epilepsia,* **2008**, *49*(6), 974-981. [http://dx.doi.org/10.1111/j.1528-1167.2007.01513.x] [PMID: 18248443]

[38] Kammersgaard, L.P.; Olsen, T.S. Poststroke epilepsy in the Copenhagen stroke study: incidence and predictors. *J. Stroke Cerebrovasc. Dis.,* **2005**, *14*(5), 210-214. [http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2005.07.001] [PMID: 17904028]

[39] Zou, S.; Wu, X.; Zhu, B.; Yu, J.; Yang, B.; Shi, J. The pooled incidence of post-stroke seizure in 102 008 patients. *Top. Stroke Rehabil.,* **2015**, *22*(6), 460-467. [http://dx.doi.org/10.1179/1074935715Z.00000000062] [PMID: 25920619]

[40] Lossius, M.I.; Rønning, O.M.; Slapø, G.D.; Mowinckel, P.; Gjerstad, L. Poststroke epilepsy: occurrence and predictors--a long-term prospective controlled study (Akershus Stroke Study). *Epilepsia,* **2005**, *46*(8), 1246-1251. [http://dx.doi.org/10.1111/j.1528-1167.2005.57904.x] [PMID: 16060935]

[41] Burn, J.; Dennis, M.; Bamford, J.; Sandercock, P.; Wade, D.; Warlow, C. Epileptic seizures after a first stroke: the Oxfordshire Community Stroke Project. *BMJ,* **1997**, *315*(7122), 1582-1587. [http://dx.doi.org/10.1136/bmj.315.7122.1582] [PMID: 9437276]

[42] Vercueil, L. Seizure and epilepsy after stroke. *Presse Med.,* **2007**, *36*(1 Pt 2), 176-181. [http://dx.doi.org/10.1016/j.lpm.2006.11.001] [PMID: 17296486]

[43] Camilo, O.; Goldstein, L.B. Seizures and epilepsy after ischemic stroke. *Stroke,* **2004**, *35*(7), 1769-1775. [http://dx.doi.org/10.1161/01.STR.0000130989.17100.96] [PMID: 15166395]

[44] Beghi, E.; D'Alessandro, R.; Beretta, S.; Consoli, D.; Crespi, V.; Delaj, L.; Gandolfo, C.; Greco, G.; La Neve, A.; Manfredi, M.; Mattana, F.; Musolino, R.; Provinciali, L.; Santangelo, M.; Specchio, L.M.; Zaccara, G.; Epistroke, G. Incidence and predictors of acute symptomatic seizures after stroke. *Neurology,* **2011**, *77*(20), 1785-1793. [http://dx.doi.org/10.1212/WNL.0b013e3182364878] [PMID: 21975208]

[45] Pitkanen, A.; Roivainen, R.; Lukasiuk, K. Development of epilepsy after ischaemic stroke. *Lancet Neurol.,* **2015**, *15*(2), 185-197. [PMID: 26597090]

[46] Roivainen, R.; Haapaniemi, E.; Putaala, J.; Kaste, M.; Tatlisumak, T. Young adult ischaemic stroke related acute symptomatic and late seizures: risk factors. *Eur. J. Neurol.,* **2013**, *20*(9), 1247-1255. [http://dx.doi.org/10.1111/ene.12157] [PMID: 23581284]

[47] Strzelczyk, A.; Haag, A.; Raupach, H.; Herrendorf, G.; Hamer, H.M.; Rosenow, F. Prospective evaluation of a post-stroke epilepsy risk scale. *J. Neurol.,* **2010**, *257*(8), 1322-1326. [http://dx.doi.org/10.1007/s00415-010-5520-9] [PMID: 20309571]

[48] Amarenco, P.; Bogousslavsky, J.; Caplan, L.R.; Donnan, G.A.; Hennerici, M.G. Classification of stroke subtypes. *Cerebrovasc. Dis.,* **2009**, *27*(5), 493-501. [http://dx.doi.org/10.1159/000210432] [PMID: 19342825]

[49] Arntz, R.; Rutten-Jacobs, L.; Maaijwee, N.; Schoonderwaldt, H.; Dorresteijn, L.; van Dijk, E.; de Leeuw, F.E. Post-stroke epilepsy in young adults: a long-term follow-up study. *PLoS One,* **2013**, *8*(2), e55498. [http://dx.doi.org/10.1371/journal.pone.0055498] [PMID: 23390537]

[50] Krakow, K.; Sitzer, M.; Rosenow, F.; Steinmetz, H.; Foerch, C.; Arbeitsgruppe, S.H. Predictors of acute poststroke seizures. *Cerebrovasc. Dis.,* **2010**, *30*(6), 584-589. [http://dx.doi.org/10.1159/000319777] [PMID: 20948201]

[51] Arntz, R.M.; Rutten-Jacobs, L.C.; Maaijwee, N.A.; Schoonderwaldt, H.C.; Dorresteijn, L.D.; van Dijk, E.J.; de Leeuw, F.E. Post-stroke epilepsy is associated with a high mortality after a stroke at young age: Follow-up of transient ischemic attack and stroke patients and unelucidated risk factor evaluation study. *Stroke,* **2015**, *46*(8), 2309-2311. [http://dx.doi.org/10.1161/STROKEAHA.115.010115] [PMID: 26138118]

[52] Waterhouse, E. Predictors of early seizures after stroke. *Epilepsy Curr.,* **2002**, *2*(3), 75-76. [http://dx.doi.org/10.1046/j.1535-7597.2002.t01-1-00028.x] [PMID: 15309149]

[53] Li, B.; Wang, L.; Sun, Z.; Zhou, Y.; Shao, D.; Zhao, J.; Song, Y.; Lv, J.; Dong, X.; Liu, C.; Wang, P.; Zhang, X.; Cui, R. The anticonvulsant effects of SR 57227 on pentylenetetrazole-induced seizure in mice. *PLoS One*. **2014**, *9*(4), e93158.

[54] Cheung, C.M.; Tsoi, T.H.; Au-Yeung, M.; Tang, A.S. Epileptic seizure after stroke in Chinese patients. *J. Neurol.,* **2003**, *250*(7), 839-843. [http://dx.doi.org/10.1007/s00415-003-1091-3] [PMID: 12883927]

[55] Leone, M.A.; Tonini, M.C.; Bogliun, G.; Gionco, M.; Tassinari, T.; Bottacchi, E.; Beghi, E.; Group, A.S. Risk factors for a first epileptic seizure after stroke: a case control study. *J. Neurol. Sci.,* **2009**, *277*(1-2), 138-142. [http://dx.doi.org/10.1016/j.jns.2008.11.004] [PMID: 19059614]

[56] Heuts-van Raak, L.; Lodder, J.; Kessels, F. Late seizures following a first symptomatic brain infarct are related to large infarcts involving the posterior area around the lateral sulcus. *Seizure,* **1996**, *5*(3), 185-194. [http://dx.doi.org/10.1016/S1059-1311(96)80034-3] [PMID: 8902919]

[57] Lamy, C.; Domigo, V.; Semah, F.; Arquizan, C.; Trystram, D.; Coste, J.; Mas, J.L. Early and late seizures after cryptogenic ischemic stroke in young adults. *Neurology,* **2003**, *60*(3), 400-404. [http://dx.doi.org/10.1212/WNL.60.3.400] [PMID: 12578918]

[58] Cleary, P.; Shorvon, S.; Tallis, R. Late-onset seizures as a predictor of subsequent stroke. *Lancet,* **2004**, *363*(9416), 1184-1186. [http://dx.doi.org/10.1016/S0140-6736(04)15946-1] [PMID: 15081649]

[59] Brigo, F.; Tezzon, F.; Nardone, R. Late-onset seizures and risk of subsequent stroke: a systematic review. *Epilepsy Behav.,* **2014**, *31*, 9-12. [http://dx.doi.org/10.1016/j.yebeh.2013.11.003] [PMID: 24291522]

[60] Benbir, G.; Ince, B.; Bozluolcay, M. The epidemiology of post-stroke epilepsy according to stroke subtypes. *Acta Neurol. Scand.,* **2006**, *114*(1), 8-12. [http://dx.doi.org/10.1111/j.1600-0404.2006.00642.x] [PMID: 16774620]

[61] Gasparini, S.; Ferlazzo, E.; Beghi, E.; Sofia, V.; Mumoli, L.; Labate, A.; Cianci, V.; Fatuzzo, D.; Bellavia, M.A.; Arcudi, L.; Russo, E.; De Sarro, G.; Gambardella, A.; Aguglia, U. Epilepsy associated with Leukoaraiosis mainly affects temporal lobe: a casual or causal relationship? *Epilepsy Res.,* **2015**, *109*, 1-8. [http://dx.doi.org/10.1016/j.eplepsyres.2014.10.012] [PMID: 25524836]

[62] De Reuck, J.; De Clerck, M.; Van Maele, G. Vascular cognitive impairment in patients with late-onset seizures after an ischemic stroke. *Clin. Neurol. Neurosurg.,* **2006**, *108*(7), 632-637. [http://dx.doi.org/10.1016/j.clineuro.2005.10.008] [PMID: 16316720]

[63] Conrad, J.; Pawlowski, M.; Dogan, M.; Kovac, S.; Ritter, M.A.; Evers, S. Seizures after cerebrovascular events: risk factors and clinical features. *Seizure,* **2013**, *22*(4), 275-282. [http://dx.doi.org/10.1016/j.seizure.2013.01.014] [PMID: 23410847]

[64] Noebels, J. Pathway-driven discovery of epilepsy genes. *Nat. Neurosci.,* **2015**, *18*(3), 344-350. [http://dx.doi.org/10.1038/nn.3933] [PMID: 25710836]

[65] Yang, H.; Song, Z.; Yang, G.P.; Zhang, B.K.; Chen, M.; Wu, T.; Guo, R. The ALDH2 rs671 polymorphism affects post-stroke epilepsy susceptibility and plasma 4-HNE levels. *PLoS One,* **2014**, *9*(10), e109634. [http://dx.doi.org/10.1371/journal.pone.0109634] [PMID: 25313998]

[66] Zhang, B.; Chen, M.; Yang, H.; Wu, T.; Song, C.; Guo, R. Evidence for involvement of the CD40/CD40L system in post-stroke epilepsy. *Neurosci. Lett.,* **2014**, *567*, 6-10. [http://dx.doi.org/10.1016/j.neulet.2014.03.003] [PMID: 24657679]

[67] Antoniades, C.; Bakogiannis, C.; Tousoulis, D.; Antonopoulos, A.S.; Stefanadis, C. The CD40/CD40 ligand system: linking inflammation with atherothrombosis. *J. Am. Coll. Cardiol.,* **2009**, *54*(8), 669-677. [http://dx.doi.org/10.1016/j.jacc.2009.03.076] [PMID: 19679244]

[68] Wallace, H.; Shorvon, S.; Tallis, R. Age-specific incidence and prevalence rates of treated epilepsy in an unselected population of 2,052,922 and age-specific fertility rates of women with epilepsy. *Lancet,* **1998**, *352*(9145), 1970-1973. [http://dx.doi.org/10.1016/S0140-6736(98)04512-7] [PMID: 9872246]

[69] Chadehumbe, M.A.; Khatri, P.; Khoury, J.C.; Alwell, K.; Szaflarski, J.P.; Broderick, J.P.; Kissela, B.M.; Kleindorfer, D.O. Seizures

are common in the acute setting of childhood stroke: a population-based study. *J. Child Neurol.,* **2009**, *24*(1), 9-12. [http://dx.doi.org/10.1177/0883073808320756] [PMID: 18923086]

[70] Suppiej, A.; Mastrangelo, M.; Mastella, L.; Accorsi, P.; Grazian, L.; Casara, G.; Peruzzi, C.; Carpanelli, M.L.; Janes, A.; Traverso, A.; Dalla, B.B. Pediatric epilepsy following neonatal seizures symptomatic of stroke. *Brain Dev.,* **2016**, *38*(1), 27-31. [http://dx.doi.org/10.1016/j.braindev.2015.05.010] [PMID: 26058328]

[71] Hauser, W.A.; Annegers, J.F.; Kurland, L.T. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935-1984. *Epilepsia,* **1993**, *34*(3), 453-468. [http://dx.doi.org/10.1111/j.1528-1157.1993.tb02586.x] [PMID: 8504780]

[72] Hui, Y.Y.; Ahmad, N.; Makmor-Bakry, M. Pathogenesis of epilepsy: challenges in animal models. *Iran. J. Basic Med. Sci.,* **2013**, *16*(11), 1119-1132. [PMID: 24494063]

[73] Kessler, K.R.; Schnitzler, A.; Classen, J.; Benecke, R. Reduced inhibition within primary motor cortex in patients with poststroke focal motor seizures. *Neurology,* **2002**, *59*(7), 1028-1033. [http://dx.doi.org/10.1212/WNL.59.7.1028] [PMID: 12370457]

[74] Sun, D.A.; Sombati, S.; Blair, R.E.; DeLorenzo, R.J. Calcium-dependent epileptogenesis in an *in vitro* model of stroke-induced "epilepsy". *Epilepsia,* **2002**, *43*(11), 1296-1305. [http://dx.doi.org/10.1046/j.1528-1157.2002.09702.x] [PMID: 12423378]

[75] Sun, D.A.; Sombati, S.; DeLorenzo, R.J. Glutamate injury-induced epileptogenesis in hippocampal neurons: an *in vitro* model of stroke-induced "epilepsy". *Stroke,* **2001**, *32*(10), 2344-2350. [http://dx.doi.org/10.1161/hs1001.097242] [PMID: 11588324]

[76] Qian, F.; Tang, F.R. Metabotropic glutamate receptors and interacting proteins in epileptogenesis. *Curr. Neuropharmacol.,* **2016**, *14*(5), 551-562. [http://dx.doi.org/10.2174/1570159X14666160331142228] [PMID: 27030135]

[77] Liu, J.; Schmitt, K.L.; Kharlamov, E.A.; Stolarski, C.J.; Grayson, D.R.; Kelly, K.M. Quantitative reverse transcription-polymerase chain reaction of GABA(A) alpha1, beta1 and gamma2S subunits in epileptic rats following photothrombotic infarction of neocortex. *Epilepsy Res.,* **2002**, *52*(2), 85-95. [http://dx.doi.org/10.1016/S0920-1211(02)00194-8] [PMID: 12458025]

[78] Kharlamov, E.A.; Kharlamov, A.; Kelly, K.M. Changes in neuropeptide Y protein expression following photothrombotic brain infarction and epileptogenesis. *Brain Res.,* **2007**, *1127*(1), 151-162. [http://dx.doi.org/10.1016/j.brainres.2006.09.107] [PMID: 17123484]

[79] Gooshe, M.; Abdolghaffari, A.H.; Aleyasin, A.R.; Chabouk, L.; Tofigh, S.; Hassanzadeh, G.R.; Payandemehr, B.; Partoazar, A.; Azizi, Y.; Dehpour, A.R. Hypoxia/ischemia a key player in early post stroke seizures: modulation by opioidergic and nitrergic systems. *Eur. J. Pharmacol.,* **2015**, *746*, 6-13. [http://dx.doi.org/10.1016/j.ejphar.2014.11.005] [PMID: 25449041]

[80] Williams, A.J.; Lu, X.M.; Slusher, B.; Tortella, F.C. Electroencephalogram analysis and neuroprotective profile of the N-acetylated-alpha-linked acidic dipeptidase inhibitor, GPI5232, in normal and brain-injured rats. *J. Pharmacol. Exp. Ther.,* **2001**, *299*(1), 48-57. [PMID: 11561062]

[81] Nazıroğlu, M. TRPV1 channel: A potential drug target for treating epilepsy. *Curr. Neuropharmacol.,* **2015**, *13*(2), 239-247. [http://dx.doi.org/10.2174/1570159X13666150216222543] [PMID: 26411767]

[82] Forsgren, L.; Bucht, G.; Eriksson, S.; Bergmark, L. Incidence and clinical characterization of unprovoked seizures in adults: a prospective population-based study. *Epilepsia,* **1996**, *37*(3), 224-229. [http://dx.doi.org/10.1111/j.1528-1157.1996.tb00017.x] [PMID: 8598179]

[83] Amano, T.; Amano, H.; Matsubayashi, H.; Ishihara, K.; Serikawa, T.; Sasa, M. Enhanced Ca^{2+} influx with mossy fiber stimulation in hippocampal CA3 neurons of spontaneously epileptic rats. *Brain Res.,* **2001**, *910*(1-2), 199-203. [http://dx.doi.org/10.1016/S0006-8993(01)02700-7] [PMID: 11489273]

[84] Neshige, S.; Kuriyama, M.; Yoshimoto, T.; Takeshima, S.; Himeno, T.; Takamatsu, K.; Sato, M.; Ota, S. Seizures after intracerebral hemorrhage; risk factor, recurrence, efficacy of antiepileptic drug. *J. Neurol. Sci.,* **2015**, *359*(1-2), 318-322. [http://dx.doi.org/10.1016/j.jns.2015.09.358] [PMID: 26671135]

[85] De Herdt, V.; Dumont, F.; Hénon, H.; Derambure, P.; Vonck, K.; Leys, D.; Cordonnier, C. Early seizures in intracerebral hemorrhage: incidence, associated factors, and outcome. *Neurology,* **2011**, *77*(20), 1794-1800. [http://dx.doi.org/10.1212/WNL.0b013e31823648a6] [PMID: 21975203]

[86] Najbauer, J.; Schuman, E.M.; Mamelak, A.N. The aspirin metabolite sodium salicylate causes focal cerebral hemorrhage and cell death in rats with kainic acid-induced seizures. *Neuroscience,* **2000**, *99*(1), 107-117. [http://dx.doi.org/10.1016/S0306-4522(00)00158-5] [PMID: 10924956]

[87] Jo, A.; Heo, C.; Schwartz, T.H.; Suh, M. Nanoscale intracortical iron injection induces chronic epilepsy in rodent. *J. Neurosci. Res.,* **2014**, *92*(3), 389-397. [http://dx.doi.org/10.1002/jnr.23328] [PMID: 24375750]

[88] Mecarelli, O.; Pro, S.; Randi, F.; Dispenza, S.; Correnti, A.; Pulitano, P.; Vanacore, N.; Vicenzini, E.; Toni, D. EEG patterns and epileptic seizures in acute phase stroke. *Cerebrovasc. Dis.,* **2011**, *31*(2), 191-198. [http://dx.doi.org/10.1159/000321872] [PMID: 21160182]

[89] Staley, K.J.; Dudek, F.E. Interictal spikes and epileptogenesis. *Epilepsy Curr.,* **2006**, *6*(6), 199-202. [http://dx.doi.org/10.1111/j.1535-7511.2006.00145.x] [PMID: 17260059]

[90] Kadam, S.D.; White, A.M.; Staley, K.J.; Dudek, F.E. Continuous electroencephalographic monitoring with radio-telemetry in a rat model of perinatal hypoxia-ischemia reveals progressive post-stroke epilepsy. *J. Neurosci.,* **2010**, *30*(1), 404-415. [http://dx.doi.org/10.1523/JNEUROSCI.4093-09.2010] [PMID: 20053921]

[91] Gelfand, J.M.; Wintermark, M.; Josephson, S.A. Cerebral perfusion-CT patterns following seizure. *Eur. J. Neurol.,* **2010**, *17*(4), 594-601. [http://dx.doi.org/10.1111/j.1468-1331.2009.02869.x] [PMID: 19968701]

[92] Koome, M.; Churilov, L.; Chen, Z.; Chen, Z.; Naylor, J.; Thevathasan, A.; Yan, B.; Kwan, P. Computed tomography perfusion as a diagnostic tool for seizures after ischemic stroke. *Neuroradiology,* **2016**, *58*(6), 577-584. [http://dx.doi.org/10.1007/s00234-016-1670-5] [PMID: 26961195]

[93] De Reuck, J.; Claeys, I.; Martens, S.; Vanwalleghem, P.; Van Maele, G.; Phlypo, R.; Hallez, H. Computed tomographic changes of the brain and clinical outcome of patients with seizures and epilepsy after an ischaemic hemispheric stroke. *Eur. J. Neurol.,* **2006**, *13*(4), 402-407. [http://dx.doi.org/10.1111/j.1468-1331.2006.01253.x] [PMID: 16643320]

[94] Gilad, R.; Lampl, Y.; Eilam, A.; Boaz, M.; Loyberboim, M. SPECT-DTPA as a tool for evaluating the blood-brain barrier in post-stroke seizures. *J. Neurol.,* **2012**, *259*(10), 2041-2044. [http://dx.doi.org/10.1007/s00415-012-6445-2] [PMID: 22323212]

[95] Miyaji, Y.; Kawabata, Y.; Joki, H.; Seki, S.; Mori, K.; Kamide, T.; Tamase, A.; Nomura, M.; Kitamura, Y.; Tanaka, F. Arterial spin-labeling magnetic resonance imaging for diagnosis of early seizure after stroke. *J. Neurol. Sci.,* **2015**, *354*(1-2), 127-128. [http://dx.doi.org/10.1016/j.jns.2015.04.049] [PMID: 25982502]

[96] Miyaji, Y.; Yokoyama, M.; Kawabata, Y.; Joki, H.; Kushi, Y.; Yokoi, Y.; Sasame, J.; Seki, S.; Mori, K.; Kamide, T.; Tamase, A.; Shima, H.; Nomura, M.; Kitamura, Y.; Tanaka, F. Arterial spin-labeling magnetic resonance imaging for diagnosis of late seizure after stroke. *J. Neurol. Sci.,* **2014**, *339*(1-2), 87-90. [http://dx.doi.org/10.1016/j.jns.2014.01.026] [PMID: 24507852]

[97] De Reuck, J.; De Groote, L.; Van Maele, G. Single seizure and epilepsy in patients with a cerebral territorial infarct. *J. Neurol. Sci.,* **2008**, *271*(1-2), 127-130. [http://dx.doi.org/10.1016/j.jns.2008.04.005] [PMID: 18495161]

[98] De Reuck, J. Management of stroke-related seizures. *Acta Neurol. Belg.,* **2009**, *109*(4), 271-276. [PMID: 20120206]

[99] Karceski, S.; Morrell, M.J.; Carpenter, D. Treatment of epilepsy in adults: expert opinion, 2005. *Epilepsy Behav.,* **2005**, *7*(Suppl 1), S1-64. quiz S65-67

[100] Huang, Y.H.; Chi, N.F.; Kuan, Y.C.; Chan, L.; Hu, C.J.; Chiou, H.Y.; Chien, L.N. Efficacy of phenytoin, valproic acid, carbamazepine and new antiepileptic drugs on control of late-onset post-stroke epilepsy in Taiwan. *Eur. J. Neurol.,* **2015**, *22*(11), 1459-1468. [http://dx.doi.org/10.1111/ene.12766] [PMID: 26148132]

[101] Belcastro, V.; Vidale, S.; Pierguidi, L.; Sironi, L.; Tancredi, L.; Striano, P.; Taborelli, A.; Arnaboldi, M. Intravenous lacosamide as treatment option in post-stroke non convulsive status epilepticus in the elderly: a proof-of-concept, observational study. *Seizure,* **2013**, *22*(10), 905-907. [http://dx.doi.org/10.1016/j.seizure.2013.07.011] [PMID: 23953988]

[102] Shetty, A.K. Prospects of levetiracetam as a neuroprotective drug against status epilepticus, traumatic brain injury, and stroke. *Front. Neurol.,* **2013**, *4*, 172. [http://dx.doi.org/10.3389/fneur.2013.00172] [PMID: 24204362]

[103] Manjarrez-Marmolejo, J.; Franco-Pérez, J. Gap junction blockers: An overview of their effects on induced seizures in animal models. *Curr. Neuropharmacol.,* **2016**, *14*(7), 759-771. [http://dx.doi.org/10.2174/1570159X14666160603115942] [PMID: 27262601]

[104] Martinc, B.; Grabnar, I.; Vovk, T. Antioxidants as a preventive treatment for epileptic process: a review of the current status. *Curr. Neuropharmacol.,* **2014**, *12*(6), 527-550. [http://dx.doi.org/10.2174/1570159X12666140923205715] [PMID: 25977679]

[105] Hawasli, A.H.; Bandt, S.K.; Hogan, R.E.; Werner, N.; Leuthardt, E.C. Laser ablation as treatment strategy for medically refractory dominant insular epilepsy: therapeutic and functional considerations. *Stereotact. Funct. Neurosurg.,* **2014**, *92*(6), 397-404. [http://dx.doi.org/10.1159/000366001] [PMID: 25359500]

[106] Scavarda, D.; Major, P.; Lortie, A.; Mercier, C.; Carmant, L. Peri-insular hemispherotomy in children with stroke-induced refractory epilepsy. *J. Neurosurg. Pediatr.,* **2009**, *3*(2), 115-120. [http://dx.doi.org/10.3171/2008.11.PEDS08218] [PMID: 19278310]

[107] Ghatan, S.; McGoldrick, P.; Palmese, C.; La Vega-Talbott, M.; Kang, H.; Kokoszka, M.A.; Goodman, R.R.; Wolf, S.M. Surgical management of medically refractory epilepsy due to early childhood stroke. *J. Neurosurg. Pediatr.,* **2014**, *14*(1), 58-67. [http://dx.doi.org/10.3171/2014.3.PEDS13440] [PMID: 24866497]