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Epilepsy in Stroke as De Novo Independent Nosology Unit – Physiology, Pathogenesis, Histology, Clinical Picture, Diagnosis, and Treatment – A Systematic Review

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Abstract

INTRODUCTION: Early seizures are considered complications of stroke, and late seizures are a type of structural epilepsy. If they are separated as a new independent nosology unit, the problem in the diagnostic – treatment approach will be solved.

PHYSIOLOGY: Cerebral blood flow is regulated by local factors such as carbon dioxide and oxygen content. Brain activity is also an important factor in the regulation of the volume speed of the blood – with locally increased neuronal activity, the local blood flow increases. Neurons in the CNS are subject to a variety of effects mediated by membrane receptors of two types – ionotropic and metabotropic.

PATHOGENESIS: Early seizures are due to transient biochemical dysfunctions, while late seizures are due to gliosis changes affecting neuronal excitability.

HISTOLOGY: The highlighted histopathological aspects confirm and support the results of clinical and radiological studies with dead nervous tissue, replaced by numerous newly formed capillaries, and surrounded by lipid-laden macrophages.

CLINICAL PICTURE: This is represented by a complex combination of excitatory epileptic manifestations and residual focal symptoms depending on the localization of the lesion.

LABORATORY DIAGNOSTICS: A very typical group of patients with post-stroke seizures have a high risk of recurrence when some of the studied biomarkers for this are available in the blood. In summary, the additional expanded package of studies of stroke patients should include screening diagnostics for the risk of epileptic seizures, namely: IL-6, IL-1β, TNF, Mg^{2+}, Ca^{2+}, CD40L, and Hsc70. IMAGING: Transient periodic MRI abnormalities have been demonstrated, possibly as a result of cerebral edema induced by seizure activity. Routine MRI in stroke patients is recommended.

TREATMENT: It is possible that rt-PA may increase the risk of early seizures after stroke. Levetiracetam (LEV) as a neuroprotective agent in stroke has been proposed as the drug of first choice, based on safety and efficacy profiles. The usual practice is to treat recurrent early-onset seizures with short-term (3–6 months) treatment with antiepileptic drugs.

CONCLUSIONS: Separation of stroke-epilepsy as a new independent nosology entity will solve the diagnostic-treatment problems in this area by changing the minimum package for laboratory tests, as well as routine MRI in patients with clinical evidence of stroke. LEV is the first-line agent for the treatment of these patients, in combination with correction of registered laboratory parameters.

Aim

The aim of this study was to justify the identification of a new nosology entity by recording the challenges in the diagnostic-treatment process of seizures in stroke and to propose solutions.

Introduction

The object of the study is early epileptic seizures in stroke. Up to now, science has had difficulty in clarifying the mechanisms of their occurrence, as well as in their management. At present, early seizures

are classified as complications of stroke, and late seizures are a type of structural epilepsy. The problem arises from the differences in the treatment-diagnostic approach in these cases, as they are not categorically positioned in any nosology unit. Nosology is the study of diseases, their classification and nomenclature, which allows solving the main tasks of private pathology and clinical medicine: knowledge of structural-functional relationships in pathology, biological, and medical bases of diseases. Therefore, it could solve the problems in this area, if seizures in stroke are considered as a new independent nosology unit. It is proposed to drop the term "post-stroke epilepsy" and introduce "stroke-epilepsy."

Physiology

Cerebral blood flow is regulated by local factors such as carbon dioxide and oxygen content. Metabolic phenomena are associated with changes in the partial pressures of oxygen and carbon dioxide. If, by means of hyperventilation, the partial pressure of carbon dioxide is reduced, cerebral blood flow is reduced, while an increase in the partial pressure of carbon dioxide increases cerebral blood flow. Brain activity is also an important factor in the regulation of the volume velocity of blood – with locally increased neuronal activity, the local blood flow is enhanced. Neurons in the CNS are subject to a variety of effects mediated by membrane receptors of two types – ionotropic and metabotropic. On stimulation by an inhibitory transmitter (GABA or glycerol), the chloride ion channel opens and potassium and chlorine flood into the neuron, reaching the resting potential (-90 mV) at which the cell has a lower concentration of sodium and chlorine. Since the neuronal membrane is 20 times more permeable to potassium than to sodium, potassium leaves by passive diffusion and large anions cannot follow them, sodium enters passively and replaces potassium, reaching the final depolarized membrane potential (-10 mV). This process is called hyperpolarization. Repolarization is the restoration of the resting state by energy-dependent active movement of sodium from the inside-out against the concentration gradient and it is replacement by potassium. The process is served by the sodium/potassium-dependent adenosine 3-phosphatase and ATP energy derived from the oxidative metabolism of sugars in the mitochondria. GABA opens chloride channels and facilitates hyperpolarization, and glutamate opens sodium channels and facilitates depolarization.

Pathogenesis

The brain's normal electrical activity is out of sync. In epileptic seizures, due to structural or functional problems in the brain, a group of neurons begin abnormally hypersynchronous emission of impulses. As a result, waves of depolarization are produced, known as paroxysmal depolarization changes [1], [2]. This is due to the prolonged depolarization of the membranes with the increased sensitivity in hypoxia and hypoglycemia. A possible mechanism for the development of epilepsy in the course of a stroke may be the down-regulation of inhibitory neural circuits after brain damage [1], [3]. In the primary damage to the brain tissue, the integrity of the brain vessels is lost. Impaired function of the blood–brain barrier, allowing substances from the blood to enter the brain, can also be a cause [4]. It also increases the release of neurotransmitters, which disrupts ion channel function and gene expression. Over a period of time, these processes lead to secondary damage, represented by chronic inflammation in the nervous tissue, gliotic conversion, angiogenesis, and abnormal synaptic plasticity, which are the cause of the formation of an epileptic focus [5]. Neurons in the amygdala and hippocampus can be such a focus in partial seizures, and in generalized seizures, these are foci in the cortex-thalamus-cortex oscillating circuit. In the primary generalized non-convulsive seizures (absences), thalamic neurons sending projections to the cortex activate GABAergic inhibition in the reticular nucleus and lead to hyperpolarization. A pacemaker current is triggered that depolarizes the membrane potential to −50mV, thereby activating potential-gated T-type calcium channels, which, further, depolarize membranes and thus induce volley discharges projecting to the cortex. Bursting activity in these circuits further augments GABAergic inhibition mediated by the reticular nucleus of the thalamus. Primary generalized or focal convulsive seizures are accompanied by changes in the membrane potential, the extracellular ionic environment, a shift of water from the extra-to intracellular space, and marked hyperemia. This leads to increased glucose consumption and acidosis with the risk of damage. The early seizures are due to transient biochemical dysfunctions, while late seizures are due to glial changes affecting neuronal excitability [6]. The excitatory neurotransmitter amino acid glutamate is also involved in the pathophysiology of symptomatic post-stroke epilepsy. It increases at the expense of the inhibitory gamma-aminobutyric acid. A disturbed balance between them leads to excitotoxicity, electrolyte imbalance, destruction of cell membranes, and release of free fatty acids [7], [8]. The seizure threshold can be lowered by the accumulation of intracellular calcium and sodium [9]. The process of epileptogenesis is slow, with a cumulative risk of 30% in the 5th year after the stroke [10], [11].

Histology

The histological specimens from patients died after showed cerebral infarct at 3 weeks from its onset as dead nervous tissue, replaced by numerous

newly formed capillaries, and surrounded by lipid-laden macrophages. The highlighted histopathological aspects confirm and support the results of clinical and radiological studies [12].

Clinical Picture

They are represented by a complex combination of excitatory epileptic manifestations and residual focal symptoms depending on the localization of the lesion.

Excitatory symptoms

They depend on the localization of the pathological process. One of the most common symptoms is due to rupture of hemorrhagic artery with cerebral hematoma and variety of excitatory symptoms of the temporal lobe. Seizures resembling transient ischemic attacks were reported in 7.1% of cases [13]. Clinically, seizures are characterized as generalized, partial, or status epilepticus.

Generalized seizures

They are characterized by bilateral simultaneous clinical and EEG manifestations, as a result of excessive discharge involving neurons from the cortex, thalamus, and reticular formation. In all generalized attacks, consciousness is necessarily disturbed; possible accompanying respiratory, circulatory, pelvic-reservoir, secretory, and other autonomic manifestations; and as well as bilaterally symmetrical tonic, clonic, tonic-clonic seizures, loss of tone, and movements (motor manifestations). Bilaterally synchronous, symmetrical, generalized EEG paroxysms. Generalized seizures account for 25% of all seizures [13].

Partial seizures

Clinical and EEG manifestations are an expression of involvement of a population of neurons located in a certain cortical (epileptogenic) area. As a result of propagation, they may evolve into another species. Partial seizures with or without secondary generalization occur in about 50% of cases, while complex partial seizures with or without secondary generalization occur in 25% of cases [13].

Epileptic status

A life-threatening condition occurring with an attack duration of more than 20 min or a series of separate attacks without recovery of consciousness between them; or expressed by continuous epileptic activity in the EEG. Children and the elderly are more prone to developing status epilepticus. It develops in up to 12% of stroke patients [13].

Waste symptoms

Depending on the cause and the place of their occurrence, they can be combined in symptom complexes in relation to the vascular blood supply, in which the disorder occurred in stroke or in relation to the brain lobe, in which the cerebral hemorrhage is located. To a large extent, they overlap, but significant differences are also noted.

Blood supplies

Cerebral infarctions in the ACA blood supply occur with contralateral to the lesion pyramidal and leg sensory disorders, frontal ataxia, pelvic-reservoir disorders, apathetic syndrome, and Moriah syndrome. Strokes in ACM blood supply proceed with pyramidal damage contralateral to the lesion with sensory disturbances of an organic type, more pronounced for the hand, contralateral lesion of the facial and sublingual nerves of the central type. Aversion of the head with looked paresis in the direction of the injury. Aphasias occurs in dominant-hemisphere damage and autotopagnosia with anosognosia in non-dominant-hemisphere damage. Strokes in ACP blood supply occur with homonymous hemianopsias, quadrantanopsias, visual agnosia, Dejerine Roussy thalamic syndrome, and alternating midbrain syndromes. Strokes in VA blood supply occur with cortical blindness, diplopia, vertigo, dysphagia, dysarthria, hemiplegia, hemianesthesia, discoordination syndrome, bulbar palsy, and alternating bridge syndromes. Strokes in BA blood supply occur with discoordination syndrome, hemianopsia, quadripyramidal syndrome to Locked in syndrome, respiratory disorders, hyperthermia, and quantitative disorders of consciousness to coma.

Cerebral lobes

They are manifested in brain hemorrhages. They have an apoplectic onset and are accompanied by arterial hypertension and meningeal syndrome with headache, nausea with vomiting, muscle rigidity, papilledema, changes in cerebrospinal fluid, and the symptoms of the corresponding brain lobe. Frontal lobe syndrome occurs with personality changes, pyramidal, pelvic, speech and olfactory disorders, and epileptic seizures. Temporal lobe syndrome occurs with auditory or olfactory hallucinations, a sense of fear, memory and speech disorders, contralateral temporal hemianopsia, and temporal epilepsy. The syndrome of the parietal lobe proceeds with sensory and motor disturbances contralaterally and epileptic seizures of Jacksonian

character by sensory or motor type. Occipital lobe syndrome presents with quadrantopsias, photopsias, and visual agnosia.

Diagnostics

Laboratory diagnostics

A very typical group of patients with post-stroke seizures have a high risk of recurrence when some of the studied biomarkers for this are available in the blood. ALDH2 rs671 polymorphism is a reliable index that can be used to predict post-stroke epilepsy [14]. The mutations of the A gene could lead to a decrease of 90% in the enzyme activity of ALDH. The mutated genes induce seizures by suppressing ALDH2 activity that may lead to decreased proteolysis of 4HN. 4-HNE serves as a specific biomarker for oxidative stress. The continuous increase of 4-HNE promotes inflammatory reactions, which enhance free radical production, increase excitability of neurons, and induce epilepsy [14], [15]. Recent studies suggest that inflammatory mediators, such as interleukin IL-1β, IL-6, and IL-10, play a significant role in the underlying pathophysiology of early seizures during stroke [16], [17], [18], [19], [20], [21], [22], [23]. The high level of tumor necrosis factor associated with the inflammatory response after stroke is an important cause of post-stroke epilepsy [24], [25], [26], [27]. Transient receptor potential cation channel subfamily M member 6 (TRPM6), belonging to non-selective cation channel families, is the key regulator responsible for the transportation of the body's Mg^{2+} balance. Serum calcium level as a possible non-epileptic cause of seizures should also be investigated. Mutation of the gene encoding TRPM6 can decrease blood magnesium levels due to the imbalanced ion transport in intestinal and kidney tubule epithelia. Some studies have reported that a homozygous variant genotype of the polymorphism of TRPM6 was associated with an increased risk of post-stroke epilepsy [28], [29]. CD40L is also thought to be a prognostic marker for unfavorable outcomes. Elevated CD40L levels were associated with a worse prognosis in post-stroke epilepsy patients [30]. The low level of heat shock protein is a biomarker that can be used in the prediction and detection of post-stroke epilepsy [31], [32]. In summary, the additional expanded package of studies of stroke patients should include screening diagnostics for the risk of epileptic seizures, namely, IL-6, IL-1β, TNF, Mg^{2+}, Ca^{2+}, CD40L, and Hsc70.

Imaging

The Alberta Stroke Program Early CT Score (ASPECTS) program is a rapid screening method for ischemic stroke patients suspected of developing symptomatic epilepsy. Research has shown that a high risk of seizures is associated with few scale points with the involvement of cortical structures [33].

Magnetic resonance imaging (MRI) is the test of choice in patients with seizures. With it is high spatial resolution, excellent intrinsic soft-tissue contrast, and lack of ionizing radiation, MRI imaging has emerged as one of the primary tools in the evaluation of seizure patients [34]. Reversible functional abnormalities have been demonstrated, possibly as a result of cerebral edema induced by seizure activity [35], [36], [37]. These abnormalities are described as transient periodic MRI abnormalities (TPMA) [38], [39]. TPMA should only be considered if two conditions are met: brain MRI signal abnormalities demonstrated periodically must be due to seizures; and second, that these abnormalities fully or partially recovered on subsequent MRI studies, as described in several papers [40], [41], [42], [43], [44], [45], [46], [47], [48], [49]. TPMA can be found in patients with seizures triggered by systemic factors such as alcohol withdrawal, infections, or post-traumatic lesions. Seizures can cause damage to gray matter structures, particularly in the thalamus and frontal lobe. The impairments of the thalamus and frontal lobe in patients with different types of seizures are different with the progression of the disease, suggesting that the influence of different epileptic seizures on the thalamocortical network is different [50]. Routine MRI in stroke patients is recommended.

Magnetoencephalography (MEG) directly measures the magnetic fields created by neural electrical activity. Unlike functional magnetic resonance imaging (fMRI), which detects a tertiary effect of neural activation (a change in local blood oxygen level due to a change in blood flow), MEG is a more direct measure of brain functional activity. The current systems are capable of speeds enabling real-time assessment of brain function. This includes normal endogenous oscillatory activity (such as alpha oscillations in the occipital lobes) and isolated "spikes" or electrical discharges in epileptic conditions, both of which require a temporal resolution measured in milliseconds. The high temporal resolution also allows the determination of the propagation of brain activity to aid in the identification of epileptogenic foci in the setting of rapid generalization.

Instrumental Diagnostics

EEG is not widely used in the diagnosis of stroke and lacks specific signs of this disease. Regardless, in acute and chronic cerebral ischemia, the lack of oxygen and metabolites causes EEG changes of different nature and intensity [51]. EEG remains the

main diagnostic method of epilepsy.

The quantitative EEG (qEEG) is a test that analyzes the brain's electrical activity to measure and display patterns that may correspond to diagnostic information and/or cognitive deficits. In 1997, the American Academy of Neurology and the American Society of Clinical Neurophysiology noted that qEEG techniques are very prone to false positives, and qEEG, except in epilepsy, should be used clinically only in concussion, and psychiatry spectrum [52]. The current guidelines from leading medical professional organizations do not recommend the use of qEEG as a screening test for neurological and psychiatric conditions.

Treatment

Recombinant tissue plasminogen activator (rt-PA) has neuroprotective but also neurotoxic effects. It is possible that rt-PA increases the risk of early seizures in stroke [53], [54], [55]. An increased risk of developing a seizure after stroke may be inherent to the therapy itself. A number of mechanisms may explain this – sudden changes in cerebral perfusion have been described as a cause of a convulsive syndrome [56], [57], [58]. When perfusion is improved by revascularization procedures, a cascade of reactions contributing to the development of the reperfusion syndrome, followed by seizures, has been suggested to be a sign of good reperfusion [59].

There is still no convincing evidence to support the use of antiepileptic drugs (AEDs) to prevent seizures after stroke. Several drugs have been suggested to have neuroprotective properties in these cases. These are valproic acid [60] and levetiracetam (LEV) [61]. Some cases of early seizures in stroke do not require specific antiepileptic therapy [6]. Post-stroke status epilepticus is an urgent indication for intravenous treatment, occurring in less than 1% of stroke patients over the next 8 years [62], but when it occurs that the mortality is high [63], [64]. The usual practice is to treat recurrent early-onset seizures with short-term (3–6 months) treatment with antiepileptic drugs [6]. Therefore, a model has been developed to identify patients at high risk of seizures: seizure occurrence with neurological deficit and/or abnormal electroencephalogram [65], [66], [67]. There is a lack of reliable evidence in the literature regarding the selection of the most appropriate AEM for the treatment of patients with stroke-epilepsy. Overall, LEV, lamotrigine, and carbamazepine appear to be effective, with LEV and lamotrigine being better tolerated than carbamazepine [68], [69], [70], [71], [72]. When choosing a drug, it is important to consider the presence of comorbid conditions. Elderly patients are particularly prone to these adverse drug effects, and therefore, it is always advisable to start with a low dose and increase slowly. The use of certain antiepileptic drugs (phenytoin, phenobarbital, and benzodiazepines) complicates recovery after stroke [6].

In the use of AEM to prevent recurrent attacks after cerebrovascular accident, LEV has been proposed as the drug of first choice, based on safety and efficacy profiles [70]. Kutlu *et al*. administered LEV monotherapy in individuals over 60 years old and a minimum of two late-onset seizures after stroke [69]. Each day, patients received doses of 1000–2000 mg, in which 82.4% of them were seizure-free, but 7 (20.6%) had side effects. These results suggest that LEV treatment is effective and well tolerated in elderly patients. Consoli *et al*. compared the efficacy of LEV treatment with that of carbamazepine (CBZ) in patients with post-stroke seizures in a multicenter, randomized, and open-label trial [71]. There was a trend toward a longer interval to first seizure recurrence in patients receiving LEV. Furthermore, LEV causes significantly less side effects than CBZ, such as deficits in attention and frontal functions. "Daily Living" activity indices were significantly poorer in patients receiving CBZ [71]. Phenobarbital treatment increases the QT-interval, probably through the modulation of sodium channels [73], [74], [75], [76], and phenobarbital is a strong inducer of CYP enzymes [77], [78].

Conclusions

Early seizures are considered complications of stroke, and late seizures are a type of structural epilepsy. If they are separated as a new independent nosology unit, the problem in the diagnostic – treatment approach will be solved. A possible mechanism for the development of epilepsy in stroke may be the downregulation of inhibitory neural circuits after brain injury, increased neurotransmitter release, impaired ion channel function, and gene expression. In summary, the additional expanded package of studies of stroke patients should include screening diagnostics for the risk of epileptic seizures, namely, IL-6, IL-1β, TNF, Mg^{2+}, Ca^{2+}, CD40L, and Hsc70. Routine MRI in stroke patients is recommended. The treatment including LEV for 3–6 months is recommended.

Authors' Contributions

C. Naydenov – Constructing the design, processing the research, coordinating the team, writing the manuscript body, overview, physiology, pathophysiology, laboratory, and instrumental diagnostic and conclusions. G. Prakova – writing the introduction.

J. Ananiev and C. Ivanova – writing the pathology. V. Mancheva – writing the clinical picture. L. Manchev – writing the imaging diagnostics. Zh. Tsokeva – writing the pharmacology treatment. A. Yordanova – language editor.

References

1. Hammer GD, McPhee SJ, editors. Pathophysiology of Disease: An Introduction to Clinical Medicine. 6th ed., Vol. 07. New York: McGraw-Hill Medical; 2010.
2. Somjen G. Ions in the Brain Normal Function, Seizures, and Stroke. New York: Oxford University Press; 2004. p. 167.
3. Goldberg EM, Coulter DA. Mechanisms of epileptogenesis: A convergence on neural circuit dysfunction. Nat Rev Neurosci. 2013;14(5):337-49. https://doi.org/10.1038/nrn3482
   PMid:23595016.
4. Oby E, Janigro D. The blood-brain barrier and epilepsy. Epilepsia. 2006;47(11):1761-74. https://doi.org/10.1111/j.1528-1167.2006.00817.x
   PMid:17116015.
5. Tanaka T, Ihara M. Post stroke epilepsy. Neurochem Int. 2017;107:217-28. https://doi.org/10.1016/j.neuint.2017.02.002
   PMid:28202284
6. Menon B, Shorvon SD. Ischaemic stroke in adults and epilepsy. Epilepsy Res. 2009;87(1):1-11. https://doi.org/10.1016/j.eplepsyres.2009.08.007
   PMid:19744830
7. Kessler KR, Schnitzler A, Classen J, Benecke R. Reduced inhibition within primary motor cortex in patients with poststroke focal motor seizures. Neurology. 2002;59(7):1028-33. https://doi.org/10.1212/wnl.59.7.1028
   PMid:12370457
8. Sun DA, Sombati S, DeLorenzo RJ. Glutamate injury-induced epileptogenesis in hippocampal neurons an *in vitro* model of stroke induced "epilepsy". Stroke. 2001;32(10):2344-50. https://doi.org/10.1161/hs1001.097242
   PMid:11588324
9. Bladin CF, Alexandrov AV, Bellavance A, Bornstein N, Chambers B, Coté R. Seizures after stroke: A prospective multicenter study. Arch Neurol. 2000;57(11):1617-22. https://doi.org/10.1001/archneur.57.11.1617
   PMid:11074794
10. Graham NS, Crichton S, Koutroumanidis M, Wolfe CD, Rudd AG. Incidence and associations of poststroke epilepsy: The prospective South London stroke register. Stroke. 2013;44(3):605-11. https://doi.org/10.1161/STROKEAHA.111.000220
    PMid:23370202
11. Chen J, Ye H, Zhang J, Li A, Ni Y. Pathogenesis of seizures and epilepsy after stroke. Acta Epileptologica. 2022;4:2. https://doi.org/10.1186/s42494-021-00068-8
12. Cuciureanu ID, Hînganu D, Stătescu C, Sava A, Hînganu MV, Turliuc MD, *et al*. Morpho-functional and radiological approach of poststroke seizures. Rom J Morphol Embryol. 2020;61(2):529-34. https://doi.org/10.47162/RJME.61.2.23
    PMid:33544805
13. De Reuck JL. Stroke-related seizures and epilepsy. Neurol Neurochir Pol. 2007;41(2):144-9.
    PMid:17530577
14. Crabb DW, Edenberg HJ, Bosron WF, Li TK. Genotypes for aldehyde dehydrogenase deficiency and alcohol sensitivity. The inactive ALDH2(2) allele is dominant. J Clin Invest. 1989;83(1):314-6. https://doi.org/10.1172/JCI113875
    PMid:2562960
15. Yang H, Song Z, Yang GP, Zhang BK, Chen M, Wu T, *et al*. The ALDH2 rs671 polymorphism affects post-stroke epilepsy susceptibility and plasma 4-HNE levels. PLoS One. 2014;9(10):e109634. https://doi.org/10.1371/journal.pone.0109634
    PMid:25313998
16. Vezzani A, Balosso S, Ravizza T. Neuroinflammatory pathways as treatment targets and biomarkers in epilepsy. Nat Rev Neurol. 2019;15(8):459-72. https://doi.org/10.1038/s41582-019-0217-x
    PMid:31263255
17. Kegler A, Caprara AL, Pascotini ET, Arend J, Gabbi P, Duarte MM, *et al*. Apoptotic markers are increased in epilepsy patients: A relation with manganese superoxide dismutase Ala16Val polymorphism and seizure type through IL-1β and IL-6 pathways. Biomed Res Int. 2020;2020:6250429. https://doi.org/10.1155/2020/6250429
    PMid:32219137
18. Liang M, Zhang L, Geng Z. Advances in the development of biomarkers for poststroke epilepsy. Biomed Res Int. 2021;2021:5567046. https://doi.org/10.1155/2021/5567046
    PMid:33959658
19. Tao H, Gong Y, Yu Q, Zhou H, Liu Y. Elevated serum matrix metalloproteinase-9, interleukin-6, hypersensitive C-Reactive protein, and homocysteine levels in patients with epilepsy. J Interferon Cytokine Res. 2020; 40(3):152-8. https://doi.org/10.1089/jir.2019.0137
    PMid:31971845
20. Jia Q, Jiang F, Ma D, Li J, Wang F, Wang Z. Association between IL-6 and seizure recurrence in patients with the first post-ischemic stroke seizure. Neuropsychiatric Dis Treat. 2020;16:1955-63. https://doi.org/10.2147/NDT.S257870
    PMid:32848401
21. van Vliet EA, Aronica E, Vezzani A, Ravizza T. Review: Neuroinflammatory pathways as treatment targets and biomarker candidates in epilepsy: Emerging evidence from preclinical and clinical studies. Neuropathol Appl Neurobiol. 2018;44(1):91-111. https://doi.org/10.1111/nan.12444
    PMid:28977690
22. Shi LM, Chen RJ, Zhang H, Jiang CM, Gong J. Cerebrospinal fluid neuron specific enolase, interleukin-1β and erythropoietin concentrations in children after seizures. Childs Nerv Syst. 2017;33(5):805-11. https://doi.org/10.1007/s00381-017-3359-4
    PMid:28236069
23. De Vries EE, van den Munckhof B, Braun KP, van Royen-Kerkhof A, de Jager W, Jansen FE. Inflammatory mediators in human epilepsy: A systematic review and meta-analysis. Neurosci Biobehav Rev. 2016;63:177-90. https://doi.org/10.1016/j.neubiorev.2016.02.007
    PMid:26877106
24. Deng X, Zhang X, Tang B, Liu H, Shen Q, Liu Y, *et al*. Design, synthesis, and evaluation of dihydrobenzo[cd]indole-6-sulfonamide as TNF-α inhibitors. Front Chem. 2018;6:98. https://doi.org/10.3389/fchem.2018.00098
    PMid:29670876
25. Bauer S, Cepok S, Todorova-Rudolph A, Nowak M, Köller M, Lorenz R, *et al*. Etiology and site of temporal lobe epilepsy influence postictal cytokine release. Epilepsy Res. 2009;86(1):82-8. https://doi.org/10.1016/j.eplepsyres.2009.05.009
    PMid:19520550
26. He LY, Hu MB, Li RL, Zhao R, Fan LH, Wang L, *et al*. The

effect of protein-rich extract from *Bombyx batryticatus* against glutamate-damaged PC12 cells via regulating γ-Aminobutyric acid signaling pathway. Molecules. 2020;25(3):553. https://doi.org/10.3390/molecules25030553
PMid:32012896

27. Shandra AA, Godlevsky LS, Vastyanov RS, Oleinik AA, Konovalenko VL, Rapoport EN, *et al*. The role of TNF-α in amygdala kindled rats. Neurosci Res. 2002;42(2):147-53. https://doi.org/10.1016/s0168-0102(01)00309-1
PMid:11849734
28. Lainez S, Schlingmann KP, van der Wijst J, Dworniczak B, van Zeeland F, Konrad M, *et al*. New TRPM6 missense mutations linked to hypomagnesemia with secondary hypocalcemia. Eur J Hum Genet. 2014;22(4):497-504. https://doi.org/10.1038/ejhg.2013.178
PMid:23942199
29. Fu CY, Chen SJ, Cai NH, Liu ZH, Zhang M, Wang PC, *et al*. Increased risk of poststroke epilepsy in Chinese patients with a TRPM6 polymorphism. Neurol Res. 2019;41(4):378-83. https://doi.org/10.1080/01616412.2019.1568755
PMid:30739590
30. 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. https://doi.org/10.1016/j.neulet.2014.03.003
PMid:24657679
31. Abraira L, Giannini N, Santamarina E, Cazorla S, Bustamante A, Quintana M, *et al*. Correlation of blood biomarkers with early-onset seizures after an acute stroke event. Epilepsy Behav. 2020;104(Pt B):106549. https://doi.org/10.1016/j.yebeh.2019.106549
PMid:31677998
32. Eriksson H, Hendén PL, Rentzos A, Pujol-Calderón F, Karlsson JK, Höglund K, *et al*. Acute symptomatic seizures and epilepsy after mechanical thrombectomy. Epilepsy Behav. 2020;104(Pt B):106520. https://doi.org/10.1016/j.yebeh.2019.106520
PMid:31526644
33. Chen Z, Churilov L, Koome ME, Yan B. Post-stroke seizures is associated with low alberta stroke program early CT score. Cerebrovasc Dis. 2017;43(5-6):259-65. https://doi.org/10.1159/000458449
PMid:28259886
34. Kushwah AP, Kedar K, Pande S. Role of MRI in evaluation of seizures. J Evol Med Dental Sci. 2011;4(105):16977-983. https://doi.org/10.14260/jemds/2015/2564
35. Goulatia RK, Verma A, Mishra NK, Ahuja GK. Disappearing CT lesions in epilepsy. Epilepsia. 1987;28(5):523-7. https://doi.org/10.1111/j.1528-1157.1987.tb03682.x
PMid:3653055
36. Sammaritano M, Andermann F, Melanson D, Pappius HM, Camfield P, Aicardi J, *et al*. Prolonged focal cerebral edema associated with partial status epilepticus. Epilepsia. 1985;26(4):334-9. https://doi.org/10.1111/j.1528-1157.1985.tb05659.x
PMid:4006892
37. Sethi PK, Kumar BR, Madan VS, Mohan V. Appearing and disappearing CT scan abnormalities in seizures. J Neurol Neurosurg Psychiatry. 1985;49(9):866-9. https://doi.org/10.1136/jnnp.48.9.866
PMid:4045480
38. Cole AJ. Status epilepticus and periictal imaging. Epilepsia. 2004;45(Suppl 4):72-7. https://doi.org/10.1111/j.0013-9580.2004.04014.x
PMid:15281962
39. Briellmann RS, Wellard RM, Jackson GD. Seizure-associated abnormalities in epilepsy: Evidence from MR imaging. Epilepsia. 2005;46(5):760-6. https://doi.org/10.1111/j.1528-1167.2005.47604.x
PMid:15857444
40. Amato C, Elia M, Musumeci SA, Bisceglie P, Moschini M. Transient MRI abnormalities associated with partial status epilepticus: A case report. Eur J Radiol. 2001;38(1):50-4. https://doi.org/10.1016/s0720-048x(00)00284-9
PMid:11287165
41. Bauer G, Gotwald T, Dobesberger J, Embacher N, Felber S, Bauer R, *et al*. Transient and permanent magnetic resonance imaging abnormalities after complex partial status epilepticus. Epilepsy Behav. 2006;8(3):666-71. https://doi.org/10.1016/j.yebeh.2006.01.002
PMid:16503204
42. Chu K, Kang DW, Kim JY, Chang KH, Lee SK. Diffusion-weighted magnetic resonance imaging in nonconvulsive status epilepticus. Arch Neurol. 2001;58(6):993-8. https://doi.org/10.1001/archneur.58.6.993
PMid:11405815
43. Kramer RE, Luders H, Lesser RP, Weinstein MR, Dinner DS, Morris HH, *et al*. Transient focal abnormalities of neuroimaging studies during focal status epilepticus. Epilepsia. 1987;28(5):528-32. https://doi.org/10.1111/j.1528-1157.1987.tb03683.x
PMid:3653056
44. Senn P, Lovblad KO, Zutter D, Bassetti C, Zeller O, Donati F, *et al*. Changes on diffusion-weighted MRI with focal motor status epilepticus: Case report. Neuroradiology. 2003;45(4):246-9. https://doi.org/10.1007/s00234-002-0850-7
PMid:12687309
45. Canas N, Breia P, Soares P, Saraiva P, Calado S, Jordão C, *et al*. The electroclinical-imagiological spectrum and long-term outcome of transient periictal MRI abnormalities. Epilepsy Res. 2010;91(2-3):240-52. https://doi.org/10.1016/j.eplepsyres.2010.07.019
PMid:20728314
46. Chan S, Chin SS, Kartha K, Nordli DR, Goodman RR, Pedley T, *et al*. Reversible signal abnormalities in the hippocampus and neocortex after prolonged seizures. AJNR Am J Neuroradiol. 1996;17(9):1725-31.
PMid:8896629
47. Huang YC, Weng HH, Tsai YT, Huang YC, Hsiao MC, Wu CY, *et al*. Periictal magnetic resonance imaging in status epilecticus. Epilepsy Res. 2009;86(1):72-81. https://doi.org/10.1016/j.eplepsyres.2009.05.011
PMid:19541453
48. Milligan TA, Zamani A, Bromfield E. Frequency and patterns of MRI abnormalities due to status epilepticus. Seizure. 2009;18(2):104-8. https://doi.org/10.1016/j.seizure.2008.07.004
PMid:18723376
49. Raghavendra S, Ashalatha R, Krishnamoorthy T, Kesavadas C, Thomas SV, Radhakrishnan K. Reversible periictal MRI abnormalities: Clinical correlates and long-term outcome in 12 patients. Epilepsy Res. 2007;73(1):129-36. https://doi.org/10.1016/j.eplepsyres.2006.10.007
PMid:17125968
50. Quan W, Xu Q, Yang F, Chen GH, Lin ZX, Zhang QR, *et al*. Impairments of gray matter in MRI-negative epileptic patients with different seizure types. Zhonghua Yi Xue Za Zhi. 2017;97(45):3524-8. https://doi.org/10.3760/cma.j.issn.0376-2491.2017.45.002
PMid:29275588
51. Binnie CD, Prior PE. Electroencephalography. J Neurol

Neurosurg Psychiatr 1994;57(11):1308-19. https://doi.org/10.1136/jnnp.57.11.1308
PMid:7964803

52. Nuwer M. Assessment of digital EEG, quantitative EEG, and EEG brain mapping: Report of the American Academy of Neurology and the American Clinical Neurophysiology Society. Neurology. 1997;49(1):277-92. https://doi.org/10.1212/wnl.49.1.277
PMid:9222209

53. Alvarez V, Rossetti AO, Papavasileiou V, Michel P. Acute seizures in acute ischemic stroke: Does thrombolysis have a role to play. J Neurology. 2013;260(1):55-61. https://doi.org/10.1007/s00415-012-6583-6
PMid:22743792

54. Keller L, Hobohm C, Zeynalova S, Classen J, Baum P. Does treatment with t-PA increase the risk of developing epilepsy after stroke. J Neurol. 2015;262(10):2364-72. https://doi.org/10.1007/s00415-015-7850-0
PMid:26205634

55. De Reuck J, Van Maele G. Acute ischemic stroke treatment and the occurrence of seizures. Clin Neurol Neurosurg. 2010;112(4):328-31. https://doi.org/10.1016/j.clineuro.2010.01.004
PMid:20133048

56. Van Mook WN, Rennenberg RJ, Schurink GW, van Oostenbrugge RJ, Mess WH, Hofman PA, *et al*. Cerebral hyperperfusion syndrome. Lancet Neurol. 2005;4(12):877-88. https://doi.org/10.1016/S1474-4422(05)70251-9
PMid:16297845

57. Hafeez F, Razzaq MA, Levine RL, Ramirez MA. Reperfusion seizures: A manifestation of cerebral reperfusion injury after administration of recombinant tissue plasminogen activator for acute ischemic stroke. J Stroke Cerebrovasc Dis. 2007;16(6):273-7. https://doi.org/10.1016/j.jstrokecerebrovasdis.2007.07.007
PMid:18035246

58. Jean WC, Spellman SR, Nussbaum ES, Low WC. Reperfusion injury after focal cerebral ischemia: The role of inflammation and the therapeutic horizon. Neurosurgery. 1998;43(6):1382-96; discussion 1396-7. https://doi.org/10.1097/00006123-199812000-00076
PMid:9848853

59. Silverman IE, Restrepo L, Mathews GC. Poststroke seizures. Arch Neurol. 2002;59(2):195-201. https://doi.org/10.1001/archneur.59.2.195
PMid:11843689

60. Gilad R, Boaz M, Dabby R, Sadeh M, Lampl Y. Are post intracerebral hemorrhage seizures prevented by antiepileptic treatment. Epilepsy Res. 2011;95(3):227-31. https://doi.org/10.1016/j.eplepsyres.2011.04.002
PMid:21632213

61. Van Tuijl JH, van Raak EP, de Krom MC, Lodder J, Aldenkamp AP. Early treatment after stroke for the prevention of late epileptic seizures: A report on the problems performing a randomised placebo-controlled double-blind trial aimed at anti-epileptogenesis. Seizure. 2011;20(4):285-91. https://doi.org/10.1016/j.seizure.2010.12.012
PMid:21277231

62. Bateman BT, Claassen J, Willey JZ, Hirsch LJ, Mayer SA, Sacco RL, *et al*. Convulsive status epilepticus after ischemic stroke and intracerebral hemorrhage: Frequency, predictors, and impact on outcome in a large administrative dataset. Neurocrit Care. 2007;7(3):187-93. https://doi.org/10.1007/s12028-007-0056-2
PMid:17503112

63. Waterhouse EJ, Vaughan JK, Barnes TY, Boggs JG, Towne AR, Kopec-Garnett L, *et al*. Synergistic effect of status epilepticus and ischemic brain injury on mortality. Epilepsy Res. 1998;29(3):175-83. https://doi.org/10.1016/s0920-1211(97)00071-5
PMid:9551779

64. Wu YW, Shek DW, Garcia PA, Zhao S, Johnston SC. Incidence and mortality of generalized convulsive status epilepticus in California. Neurology. 2002;58(7):1070-6. https://doi.org/10.1212/wnl.58.7.1070
PMid:11940695

65. Kim LG, Johnson TL, Marson AG, Chadwick DW, MRC MESS Study group. Prediction of risk of seizure recurrence after a single seizure and early epilepsy: Further results from the MESS trial. Lancet Neurol. 2006;5(4):317-22. https://doi.org/10.1016/S1474-4422(06)70383-0
PMid:16545748

66. Strzelczyk A, Haag A, Raupach H, Herrendorf G, Hamer HM, Rosenow F. Prospective evaluation of a post-stroke epilepsy risk scale. J Neurol. 2010;257(8):1322-6. https://doi.org/10.1007/s00415-010-5520-9
PMid:20309571

67. Kim HJ, Park KD, Choi KG, Lee HW. Clinical predictors of seizure recurrence after the first post-ischemic stroke seizure. BMC Neurol. 2016;16(1):212. https://doi.org/10.1186/s12883-016-0729-6

68. Gilad R, Sadeh M, Rapoport A, Dabby R, Boaz M, Lampl Y. Monotherapy of lamotrigine versus carbamazepine in patients with poststroke seizure. Clin Neuropharmacol. 2007;30(4):189-95. https://doi.org/10.1097/WNF.0b013e3180333069
PMid:17762314

69. Kutlu G, Gomceli YB, Unal Y, Inan LE. Levetiracetam monotherapy for late poststroke seizures in the elderly. Epilepsy Behav. 2008;13:542-4. https://doi.org/10.1016/j.yebeh.2008.04.025
PMid:18539085

70. Belcastro V, Costa C, Galletti F, Autuori A, Pierguidi L, Pisani F, *et al*. Levetiracetam in newly diagnosed late-onset post-stroke seizures: A prospective observational study. Epilepsy Res. 2008;82(2-3):223-6. https://doi.org/10.1016/j.eplepsyres.2008.08.008
PMid:18829259

71. Consoli D, Bosco D, Postorino P, Galati F, Plastino M, Perticoni GF, *et al*. Levetiracetam versus carbamazepine in patients with late poststroke seizures: A multicenter prospective randomized open-label study. Cerebrovasc Dis. 2012;34(4):282-9. https://doi.org/10.1159/000342669
PMid:23128439

72. Huang YH, Chi NF, Kuan YC, Chan L, Hu CJ, Chiou HY, *et al*. Efficacy of phenytoin, valproic acid, carbamazepine and new antiepileptic drugs on control of lateonset post-stroke epilepsy in Taiwan. Eur J Neurol. 2015;22(11):1459-68. https://doi.org/10.1111/ene.12766
PMid:26148132

73. Nilsson L, Bergman U, Diwan V, Farahmand BY, Persson PG, Tomson T. Antiepileptic drug therapy and its management in sudden unexpected death in epilepsy: A case-control study. Epilepsia. 2001;42(5):667-73. https://doi.org/10.1046/j.1528-1157.2001.22000.x
PMid:11380576

74. Schwarz JR, Bromm B, Ochs G. Phenobarbital induces slow recovery from sodium inactivation at the nodal membrane. Biochim Biophys Acta. 1980;597(2):384-90. https://doi.org/10.1016/0005-2736(80)90114-5
PMid:6245694

75. Siniscalchi A, Gallelli L, Calabro G, Tolotta GA, De Sarro G. Phenobarbital/lamotrigine coadministration-induced blood

dyscrasia in a patient with epilepsy. Ann Pharmacother. 2010;44(12):2031-4. https://doi.org/10.1345/aph.1P335
PMid:21098752

76. Siniscalchi A, Gallelli L, De Sarro G, Malferrari G, Santangelo E. Antiepileptic drugs for central post-stroke pain management. Pharmacol Res. 2012;65(2):171-5. https://doi.org/10.1016/j.phrs.2011.09.003
PMid:21925602

77. Kennedy WK, Jann MW, Kutscher EC. Clinically significant drug interactions with atypical antipsychotics. CNS Drugs. 2013;27(12):1021-48. https://doi.org/10.1007/s40263-013-0114-6
PMid:24170642

78. Landmark CJ, Patsalos PN. Drug interactions involving the new second-and third-generation antiepileptic drugs. Expert Rev Neurother. 2010;10(1):119-40. https://doi.org/10.1586/ern.09.136
PMid:20021326