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Post – Stroke Seizures: A Comprehensive Review of Epidemiology, Pathophysiology, Risk Factors, Clinical Spectrum and Outcomes

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ABSTRACT

Post – stroke seizure (PSS) represent a significant and often notable complication following cerebrovascular damage due to infarct and hemorrhage, that can affect stroke recovery and the long-term prognosis. This review aims to delineate the epidemiology, clinical spectrum, and outcomes of PSS through an extensive analysis of current literature. It is classified into two types based on the onset of occurrence following stroke, early-onset, occurring within the first seven days following stroke, and late-onset, which manifest beyond seven days after stroke. Early seizures have the same clinical course as acute symptomatic seizures, they rarely recur or require long – term antiepileptic drugs (AED's). Conversely, late seizures are associated with a risk of recurrence similar to that of unprovoked seizures in a patient with a focal lesion, thereby requiring long – term administration of AED's. The pathophysiology of PSS is multifaceted and involves a complex interplay of acute metabolic disturbances, excitotoxic neurotransmitter release causing neuronal hyperexcitability, and chronic neural network reorganization. Key risk factors include the type, location, and severity of the stroke, with cortical and hemorrhagic strokes being more prone to induce seizures. Clinically, PSS manifests predominantly as focal seizures, with some cases progressing to generalized seizures or status epilepticus. PSS is associated with poorer functional recovery, reduced quality of life, cognitive decline, increased morbidity, and a higher risk of developing epilepsy. Preventing stroke and PSS remains a cornerstone of any strategy to achieve optimal brain health. Early identification and appropriate management of PSS are crucial for minimizing their impact and thereby improving long – term outcomes for stroke survivors. Effective management includes the use of AED's, secondary prevention strategies, comprehensive rehabilitation, and regular monitoring. Continued research and individualized treatment plans are essential to develop better preventive, diagnostic, and therapeutic strategies for PSS, ultimately enhancing the prognosis and wellbeing of those affected by strokes.

Keywords: post-stroke seizure, complication, stroke, morbidity, epilepsy, anti-epileptic drugs.

Introduction

Stroke is the most prevalent cause of seizures and epilepsy in elderly population[1]. With an annual death toll of around 5.5 million, stroke continues to be the second most common cause of mortality worldwide and is the primary cause of disability worldwide, impacting 50% of survivors of stroke. Ischemic strokes generally represent around 80% of stroke occurrences, whereas hemorrhagic strokes account for about 20%[2,3]. The occurrences of stroke have surged by 50% in the last twenty years, showing a 70% rise in the incidence from 1990 to 2019[4]. The development of post-stroke seizure (PSS) affects 2% to 14% of those who survive an ischemic stroke and 10% to 20% of those who have suffered a hemorrhagic stroke[5]. The latency period for the onset of post-stroke seizure is inconsistent, yet 40% to 80% of the cases manifest within the first year following a stroke[5]. In addition to rising mortality and morbidity in stroke patients, post-stroke seizures leads to prolonged stay in the hospital and greater disability during discharge when compared to stroke patients without post – stroke seizure[6]. The occurrence of seizures shortly after a stroke can exacerbate metabolic stress and neuronal damage, leading to an increase in the size of infarct, higher mortality, and detrimental functional outcomes[7,8]. Repeated episodes of seizures can result in injuries, disrupt the cognitive function, hinder one's ability to perform their activities of daily living (ADL), and adversely impact the quality of life[9,10]. This review encapsulates the current insights into post-stroke epileptogenesis, clinical spectrum, and treatment which includes both primary and secondary prophylactic measures, and suggests strategies to enhance research efforts.

Classification

Acute symptomatic seizures resulting from a stroke are strongly linked to the location and extent of brain damage. Consequently, a causal relationship can be established if the brain lesion responsible for the seizures is clearly identified and the seizure happens in close temporal proximity[11]. The International League Against Epilepsy (ILAE) categorizes post – stroke seizures as early or late based on a 7 – day threshold. According to this classification, seizures that occur within 7 days from the onset of stroke are considered early seizures, while those occurring 7 days after the onset of stroke are classified as late seizures[12]. Early seizures are distinguished by amplified inflammatory responses, alterations in neuronal signalling associated with protein synthesis, enhanced release of excitatory neurotransmitters such as glutamate, ionic dysregulation, increased permeability of the blood-brain barrier (BBB), degradation of membrane phospholipids, liberation of free fatty acids, and heightened oxidative stress[13,14]. Additionally, the adjacent ischemic penumbra, which is characterized by its electrical irritability, serves as a zone of epileptogenesis[15]. Late seizures, in contrast are delineated by immutable alterations, including selective neuronal depletion, gliosis, chronic inflammation, neurodegeneration, angiogenesis, collateral synaptic arborization, and modifications in synaptic plasticity[13]. These modifications culminate in neuronal hyperexcitability, neuronal hypersynchrony, and an augmented propensity for seizures[16]. Thus, early seizures adhere to the trajectory of acute symptomatic seizures, while late seizures align with the progression of unprovoked seizures[17,18,19]. Hence, categorizing post – stroke seizures into early and late types is essential for differentiating between acute symptomatic and unprovoked seizures.

Epidemiology

The preponderance of strokes transpires in adults over 45 years of age, with up to 90% being ischemic and the remainder hemorrhagic. Stroke represents the most prevalent discernible etiology of acquired epilepsy in high – income nations[20,21]. Epilepsy risk assessments following stroke have been thoroughly investigated, with findings varying according to study methodologies. In the general populace, the most representative estimates

are derived from prospective longitudinal studies of large cohorts or register based analyses. An incidence rate of post stroke epilepsy of 6.4% was identified in both a population – based study in London, UK, and a nationwide registry in Sweden[22,23]. Post – stroke epilepsy (PSE) emerged in 3.8% of individuals within 5 years following the onset of their initial stroke in the Oxfordshire Community Stroke Project[24]. Similarly, in the prospective Seizures After Stroke Study, which observed 1,897 patients for 9 months, post – stroke epilepsy developed in 2.5% of participants[25]. Additionally, the Rochester study, encompassing 535 individuals with ischemic strokes, reported a 3.4% incidence of post-stroke epilepsy over a 5.5-year follow-up period[26]. In adult demographics, approximately 70 – 85% of cerebrovascular maladies are ischemic, and the preponderance of post-stroke epilepsy cases results from arterial ischemic stroke[27]. The most extended population – based longitudinal study conducted by Graham and associates disclosed that the 10 – year prevalence of post-stroke epilepsy was 28.7% following total anterior circulation infarct, 13.4% following partial anterior circulation infarct, and 4.8% following posterior circulation infarct[22]. Following an ischemic stroke, the highest risk for the initial unprovoked post – stroke seizure occurred during the first year of follow – up[19,28]. During a follow-up period of 5 years, the average annual increase in risk for late seizures post ischemic stroke after the initial year was 1.5%[24]. A further investigation disclosed that the probability of yearly incidence of seizures subsequent to a primary ischemic stroke is 6.3%, 2.4%, 1.3% after the first, second and third year following the stroke respectively and 0.3% henceforth[29]. Registry derived data from a case – control investigation likewise implied that the likelihood of spontaneous seizure occurrence remains elevated for 7 years following an ischemic stroke, peaking during the initial year post stroke[30]. Data accumulated over the past decade has highlighted the emergence of post-stroke epilepsy in younger adults[19,28,29]. Moreover, within the Rochester cohort of ischemic stroke patients, the unequivocal risk of late-onset seizures post-ischemic stroke was analogous between individuals under 55 years of age and those exceeding 75 years of age[26]. The minimal influence of age on the susceptibility to post-stroke epilepsy was similarly observed in two contemporary investigations[31]. Caveats also persist concerning the identification of seizures in the geriatric population (above 60 years), in whom ictal episodes may be less prevalent and seizure phenotypes are more challenging to discern compared to younger individuals (below 55 years)[32]. The diagnostic scrutiny is also expected to be more exhaustive in younger individuals with ischemic stroke compared to the elderly, and the elevated survival rates among younger cohorts may underpin the prevalence of late – onset seizures[33]. The prevalence of acute symptomatic seizures and unprovoked seizures fluctuates across disparate studies, partly owing to heterogenous research methodologies, divergent delineations of the temporal spans for acute symptomatic and unprovoked seizures, and inconsistent follow-up intervals. The occurrence of acute symptomatic seizures has been documented to range from 2% to 33%, however, it is consistently observed that over half of these seizures transpire within the initial 24 hours post-stroke[16,25]. The prevalence of unprovoked seizures ranges from 3% to 67%. These seizures are more frequently observed between 6 and 12 months post – stroke, although unprovoked seizures can still manifest even a decade after the event of stroke[16,25].

Pathophysiology

In the context of ischemic stroke, early seizures are correlated with elevated extracellular potassium and glutamate levels, consequent to ischemic neuronal injury, thereby amplifying neuronal excitation. Conversely, late seizures arise from gliotic scarring within the cortex, dysregulation of the neurovascular unit, and perturbation of neuronal networks[34]. In preclinical research,

cerebrovascular accidents trigger inflammatory cascades that facilitate epileptogenesis. Stimulated astrocytes and microglia, alongside the secretion of proinflammatory cytokines (such as Interleukin [IL] – 1β and High mobility group protein B1), exacerbate blood-brain barrier (BBB) compromise, leading to the release of albumin and activation of the Transforming growth factor (TGF) – β pathway, thus setting off a detrimental feedback loop[34]. These investigations have exclusively explored the acute phase of stroke, thus leaving the mechanisms by which the progression to epileptogenesis is ambiguous. Hemorrhagic stroke leads to the extravasation of albumin into the cerebral parenchyma, which triggers epileptogenesis through the activation of the transforming growth factor-β receptor on astrocytes. This phenomenon is orchestrated by a distinctive inflammatory milieu and the genesis of excitatory synapses[35]. Pathogenic impact has also been ascribed to the extravasation of additional hematogenous substances, such as hemosiderin or iron[36]. Post-stroke epilepsy is more prevalent in hemorrhagic than ischemic strokes, indicating the potential involvement of iron accumulation in post-stroke epileptogenesis[36]. Iron is a micronutrient which is crucial for mitochondrial activity[36]. In healthy individuals, approximately 4–5 grams of iron are sequestered primarily within erythrocytes and the liver. Iron within the cerebral milieu is meticulously regulated to sustain neuronal homeostasis[36]. Stroke perturbs this balance, leading to iron deposition within the brain parenchyma (e.g., intracerebral hemorrhage or hemorrhagic transformation following ischemic stroke) or on the surface (e.g., subarachnoid hemorrhage), which is profoundly cytotoxic[36]. The recently elucidated iron-dependent cellular demise, termed ferroptosis, is ascribed to lipid peroxidation instigated by the generation of reactive oxygen species. Excessive iron accumulation is observed in a range of neurologic pathologies, including epilepsy. Persistent perturbations in neuronal excitability may arise due to hemosiderin deposits, culminating in post – intracerebral hemorrhage (ICH) inflammation and gliotic changes[36]. Cortical superficial siderosis exhibits a robust correlation with post-stroke epilepsy[37]. Furthermore, delayed seizures following intracerebral hemorrhage are linked specifically to lobar cerebral microbleeds and the APOEe4 genotype, implying the concurrent presence of cerebral amyloid angiopathy pathology in post-stroke epilepsy[38]. A recent investigation divulged that cortical superficial siderosis serves as a predisposing element for the onset of seizures in the context of cerebral amyloid angiopathy[39]. Cortical superficial siderosis confined to the convex surfaces of the cerebral hemispheres and the supratentorial area may present as transient focal neurological events (TFNEs; i.e., amyloid episodes), which are predominantly recurrent, patterned, and brief (typically less than 30 minutes) with diverse clinical manifestations[40]. Transient focal neurological episodes are observed in 34% of individuals with cerebral amyloid angiopathy and cortical superficial siderosis, frequently recurring in 53% of cases, with 4% progressing to generalized convulsions[40]. Cortical superficial siderosis has the potential to provoke spontaneous convulsions in the absence of alternative causes, indicating its involvement in post-stroke epileptogenesis[36].

Risk Factors

Attributable to the diverse etiologies and pathologies, the engagement of cerebrovascular risk determinants is variegated. Nonetheless, substantial infarct volume, involvement of cortex, magnitude of cerebrovascular accident, hemorrhagic insult or infarct with hemorrhagic transformation, and premature convulsions are unequivocal prognosticators of post-stroke epilepsy[34,41]. The incidence of acute convulsive episodes associated with hemorrhagic stroke surpasses that of ischemic cerebrovascular events (10–16% vs. 2–4%)[42,43]. Ischemic infarctions accompanied by hemorrhagic conversion exhibit an elevated convulsion risk compared to isolated ischemic strokes[44]. There exists an augmented frequency of post-stroke

epilepsy in instances involving the cortex, extensive infarction of anterior circulatory territory, severe cerebrovascular events with extensive lesions, and functional impairments[5,45]. Reperfusion insult may present as disruption of the blood – brain barrier, cortical excitation, and epileptic episodes[46]. Cerebrovascular interventions, encompassing craniotomy, decompressive craniectomy, administration of intravenous alteplase, or endovascular therapy, are likewise regarded as post-stroke epilepsy predisposition factors. Nonetheless, this observation was not corroborated in other investigations, including extensive population – based stroke registries and meticulously designed multi center studies, which found no association between early convulsions or post-stroke epilepsy and reperfusion therapies, whether intravenous thrombolysis alone or in conjunction with mechanical thrombectomy[47]. Variations in the intensity or site of hemorrhagic transformation and the permeability of recanalized vessels may influence the manifestation of convulsions subsequent to ischemic cerebrovascular incidents[48]. A comprehensive meta-analysis encompassing 51 investigations elucidated that irrespective of whether individuals afflicted by ischemic stroke receive thrombolysis or thrombectomy, hemorrhagic transformation exhibited a pronounced correlation with the onset of early seizures and post stroke epilepsy[48]. Recanalization therapy in individuals afflicted by stroke may partially salvage moribund neurons, resulting in the formation of sporadic islands of the cortex[49]. These surviving residual islands could conceivably influence epileptogenesis in conjunction with hemorrhagic transformation[49]. Acute symptomatic seizures may be precipitated by direct and instantaneous factors, such as metabolic disturbances, infections of the central nervous system, septicemia, physical injuries, pharmacological substances, and ethanol consumption[50,51]. Seizures that are acute and symptomatic, caused by metabolic imbalances, are linked to the rate at which the metabolic condition worsens, quicker rate of decline increases the likelihood of seizures[52]. Symptomatic convulsions stemming from a central nervous system infection may still be classified as acute symptomatic seizures beyond 7 days, contingent upon the clinical progression or laboratory diagnostics, as the delineation remains ambiguous[11]. Septicemia can precipitate encephalopathy, which engenders convulsive or nonconvulsive seizures by activating the neural circuits that facilitate seizure activity[53]. Acute symptomatic seizures attributable to alcohol withdrawal should be contemplated in an individual with a background of substantial ethanol consumption who manifests generalized tonic – clonic seizures following a period of alcohol abstinence lasting 7 – 48 hours[11]. Alterations linked to small vessel pathology, encompassing leukoaraiosis and lobar cerebral microbleeds, are correlated with post-stroke epilepsy[38,54]. Cortical superficial siderosis exhibits a robust correlation with post-stroke epilepsy, irrespective of whether the cerebrovascular insult is ischemic or hemorrhagic, and is marked by the deposition of hemosiderin in the pial or subpial strata of the central nervous system[37]. In subarachnoid hemorrhage (SAH), cortical superficial siderosis bears a significant association with post-stroke epilepsy, irrespective of location of the aneurysm, intensity of SAH, or cerebrovascular symptoms[55]. Additionally, an extension of intracerebral hemorrhage into the subarachnoid space is notably linked to the occurrence of early seizures, regardless of the site of hematoma[56]. In adults, Jungehulsing et al., discerned that hypertension and the intensity of cerebrovascular insult were substantial prognosticators for post-stroke epilepsy[57]. Remarkably, as per the findings of Devuyst et al., an augmented concentration of cholesterol might exert a salutary effect on convulsions and ischemic cerebrovascular events[58]. Furthermore, Roivainen et al., observed that nicotine use, chronic alcohol indulgence, and pre – stroke infections were more pronounced in individuals experiencing late post stroke seizures

compared to those with acute symptomatic convulsions (up to 7 days following the onset of the stroke)[29]. Remarkably intriguing findings were elucidated by Cordonnier et al., who established that antecedent cognitive impairment was independently associated with the onset of delayed convulsions, but not with early epileptic episodes[59]. This observation might be elucidated by a potential disruption in glutamatergic pathways among individuals with dementia. Hesdorffer et al., discerned that the propensity for subsequent spontaneous unprovoked seizures is elevated in instances of late post-stroke seizures compared to early symptomatic epileptic episodes[17]. The outcomes of a Korean investigation revealed that certain determinants of elevated susceptibility to a secondary convulsion following an initial episode may materialize; individuals predominantly at risk for a subsequent seizure during follow-up are typified by male sex, age under 65 years, extensive ischemic lesions, and focal seizures in clinical manifestations[60]. This insight could prove beneficial in formulating personalized treatment strategies following the initial seizure. Recent studies also indicate that intravenous recombinant tissue plasminogen activator (rTPA) therapy, sanctioned for the management of acute cerebrovascular accident, may constitute a risk factor for subsequent post-stroke epilepsy due to its potential neurotoxic effects[61]. The utilization of antidepressants was a notable predisposing factor for late post-stroke seizures within the Finnish cohort, whereas the administration of antipsychotic or anxiolytic pharmacological agents was characteristic of patients exhibiting both acute symptomatic seizure and late post-stroke seizure[29]. As a matter of fact, a familial antecedent of epilepsy is ought to be considered as a contributing risk factor for post-stroke epilepsy, given that genetic predispositions play a role in epileptogenesis[6].

Clinical Spectrum

Post – stroke seizures predominantly exhibit localization specific seizure semiology, contingent upon the precise locus of the cerebral lesion. Approximately one – third of all seizures are generalized tonic clonic seizures (GTCS), while the remaining two – thirds present as focal seizures, with status epilepticus noted in 9% of instances[62,63]. Focal seizures are prevalent in the acute phase of seizure onset, whereas generalized seizures are more frequent in the chronic phase[62]. Among patients with ischemic cerebrovascular accidents resulting from occlusion of large vessel, seizures emerging within the initial 24 hours were chiefly focal convulsions or GTCS, whereas seizures accompanied by impaired awareness tend to occur more frequently beyond 24 hours[64]. Conrad et al., demonstrated that in nearly 41% of post stroke seizure subjects, seizures were categorized as partial (predominantly simple partial), while 57% of individuals experienced generalized seizures. Nonetheless, there remain cases where the specific type of convulsion remains indeterminate[65]. In instances of post stroke seizures in the pediatric population, Kopyta et al., revealed that every analysed juvenile subject with post-stroke seizures experienced convulsions, which were focal in character. Nevertheless, in 40% of these cases, the convulsions were secondary generalized[66]. In the investigation conducted by Pilarska and Lemka, 7% of the scrutinized pediatric patients with acute ischemic stroke exhibited early post-stroke seizure, that were generalized tonic & clonic, manifesting within the initial 24 hours post cerebrovascular accident[67]. The incidence rates of epilepsy, stratified by age, have shifted, exhibiting a reduction in younger demographics and a surge among individuals over 60 years[68]. Cerebrovascular accidents (CVA) emerge as the foremost etiology of epilepsy in patients beyond 60 years of age, with an incidence ranging from 2 to 4% as reported in various studies[69]. Early seizures manifest considerably more frequently in individuals with hemorrhagic strokes and are associated with a dismal prognosis, accompanied by elevated mortality rate in the hospital, however, the recurrence rate remains minimal. Late seizures

predominantly emerge between 6 to 24 months post stroke, with a heightened recurrence rate[70]. The delayed onset of the initial convulsion serves as an autonomous predisposing factor for epilepsy following an ischemic stroke, but not subsequent to hemorrhagic stroke[71]. About 20% of convulsions occurring in individuals with a prior cerebral infarction may subsequently manifest as a clinical indication of a new cerebrovascular event[70]. Arboix et al., postulated that individuals at the greatest risk of manifesting epileptic seizures are elderly patients with extensive hemorrhagic infarctions in the parietal lobe, who may warrant prophylactic management with antiepileptic agents for a brief duration[72]. Epilepsy seldom constitutes a major issue in young individuals recovering from cryptogenic ischemic strokes[68]. Dhanuka et al., discovered a more youthful median age at the initial convulsion post cerebrovascular accident (mean 45.41 years), despite enrolling a diverse cohort (age ranging between 5 months to 76 years)[73]. In this compilation, the males were observed with greater frequency relative to females, which were consistent with antecedent regional and global studies[73]. The majority of post-stroke seizures exhibit a focal onset and predominantly fall into the category of simple partial seizures, which is succeeded by primary generalized seizures. Complex partial seizures (CPS) are less prevalent, with the highest documented incidence being 24% of all post-stroke seizures[74,75]. In the investigation undertaken by Kamble et al., the predominant category of convulsion was generalized, in contrast to partial or secondary generalized seizures typically anticipated in symptomatic epilepsy such as post-stroke seizures[76]. This finding diverges from earlier data indicating a predominance of partial seizures in post-stroke seizures, which may be attributable to the low educational attainment of the study cohort, potentially leading to a misclassification of partial or secondary generalized seizures as generalized[75]. In an investigation from India conducted by Dhanuka et al., 60% of post-cerebrovascular accident patients exhibited recurrent convulsions[73]. Nonetheless, certain inquiries revealed lower frequencies of recurrent seizures, such as in the prospective multicentric global investigation Seizures After Stroke Study Group (SASS), where 28% of participants experienced multiple convulsions[77]. The prevalence of Status Epilepticus varies across studies. Milandre et al., documented an incidence of 14% among patients with initial post-stroke epilepsy, whereas Lo et al., reported a prevalence of 10%[78,79].

Outcomes

In advanced nations, no fewer than one in ten cerebrovascular accident survivors will experience epilepsy[80]. Nevertheless, despite the elevated risk of convulsions and epilepsy following a stroke, the American Heart Association does not advocate for prophylactic intervention with antiepileptic drugs (AEDs) in these patients[81]. The potential utility of certain novel – generation AEDs in thwarting epileptogenesis is currently under speculation. In a rodent paradigm of epilepsy, levetiracetam attenuated gliosis within the hippocampus and piriform cortex[82]. Subsequently, Perampanel, an innovative selective, non – competitive AMPA glutamate receptor antagonist, was proposed as a prospective impediment of epileptogenesis by mitigating glutamatergic excitotoxicity[83]. Moreover, aspirin and rapamycin, owing to their anti-inflammatory properties, are contemplated for their potential in the prophylaxis of post-stroke epilepsy[84,85]. Prophylactic administration of primary antiepileptic drugs is not endorsed, as its efficacy in mitigating acute symptomatic or idiopathic convulsions or enhancing functional outcomes and survival rates remains inadequately substantiated[45]. Short – term AEDs therapy, spanning 1 to 4 weeks, is generally employed for acute symptomatic seizures due to the minimal risk of recurrence[45]. European directives do not advocate for secondary prophylactic AEDs intervention for post-stroke seizures. Individuals undergoing a solitary acute symptomatic convulsion within 7 days possess a 10

– 20% probability of encountering subsequent acute symptomatic seizures, hence secondary AEDs prophylaxis is deemed unnecessary[45,86]. Notwithstanding the comparatively modest recurrence rate, ephemeral antiepileptic agent therapy is employed in individuals with a pathophysiological substrate. Antiepileptic agents may attenuate neuronal excitotoxicity, peri-infarct depolarization, and inflammatory cascades[87]. Certain investigations advocate for transient antiepileptic agent therapy in nascent seizures to mitigate the proclivity for clinical deterioration during the acute phase. This strategy is predicated on pathophysiological considerations, encompassing diminished cerebral perfusion states such as stroke with hemodynamically significant stenosis, cerebral edema, and vasospasm subsequent to SAH[88,89]. Nevertheless, guidelines advocate for the gradual reduction of antiepileptic agent therapy following the acute phase due to the low 10 – year probability of idiopathic unprovoked convulsion occurrence post a solitary post-stroke seizure which constitutes about 30%[45]. The likelihood of recurrent idiopathic post-stroke seizures within a decade is elevated (70%), consequently prophylaxis with secondary AEDs is endorsed[17,45]. Prolonged AEDs administration is advised for post – cerebrovascular unprovoked idiopathic seizures due to the substantial likelihood of recurrence of seizure upon cessation of therapy which estimates ≥50%[17,45]. In summation, protracted AEDs utilization is contraindicated, except in cases of idiopathic unprovoked post-stroke seizures. Nonetheless, it may be employed transiently during the acute phase, contingent upon the patient's condition, in alignment with the conceptualization and therapeutic paradigm for epilepsy delineated by the International League Against Epilepsy (ILAE)[11,90]. A multicentric randomized controlled trial posited that lamotrigine exhibits superior efficacy as a primary therapeutic agent for individuals with focal epilepsy compared to zonisamide or levetiracetam[91]. Concerning the management of post – stroke seizures, the efficacies of lamotrigine, levetiracetam, and carbamazepine (extended – release) were analogous, although lamotrigine and levetiracetam were deemed more tolerable relative to carbamazepine[92,93]. The deployment of a vigorous statin regimen in individuals afflicted by cerebrovascular accidents has been reported to mitigate the incidence of both early and delayed post-stroke seizures. Additionally, prolonged administration of statins for durations exceeding 2 years resulted in a diminution of the risk for post-stroke epilepsy, irrespective of whether the statin therapy was commenced pre or post the event of cerebrovascular accident[94,95]. The exact anticonvulsant mechanism of statins remains enigmatic, though numerous hypotheses have been posited. Primarily, neuroinflammation consequent to cerebrovascular accidents amplifies neuronal excitability, precipitating the release of aberrant neurotransmitters through augmented blood-brain barrier (BBB) permeability, thereby inducing seizures via the exacerbation of cerebral hypoxia[96]. Statins mitigate convulsions by deploying anti-inflammatory effects, including the modulation of BBB permeability, regulation of endothelial nitric oxide synthase, attenuation of proinflammatory gene expression, inhibition of pro-inflammatory cytokines and reactive oxygen species, and suppression of lipid peroxidation[97]. Although acute ischemia augments glutamate concentrations, statins attenuate the excitotoxicity of glutamate by diminishing the activity and uptake of N-methyl-D-aspartate (NMDA) receptors and modulating intracellular calcium concentrations[96,98,99]. Apoptosis is precipitated by Bax, whereas Bcl suppresses it. Statins influence apoptotic cascades linked to these genes and enhance the neuronal viability, thus forestalling epilepsy[13]. As per study conducted by Tanaka et al., 33% of medical facilities dispense AEDs following the initial late convulsion, whereas 88% prescribe AEDs after a subsequent episode[34]. An exception pertains to patients exhibiting status epilepticus as their initial epileptic presentation[90]. Although the prompt deployment of anti-epileptic drugs in post CVA

individuals does not alter the etiology or prognostic trajectory of the affliction, it may avert the manifestation of a subsequent convulsion, particularly given the substantial risk of recurrence following an initial late – onset post – stroke seizures, which is approximated to impact roughly one – third of patients[60,100]. Conversely, in the investigation conducted by Ahangar et al., phenobarbital or phenytoin was administered at a nascent stage, specifically to each subject presenting with both early - and late - onset post – stroke seizures[101]. The researchers attribute the subsequently diminished frequency of recurrent convulsions to this precocious incorporation of anticonvulsant therapy[101]. According to studies, anticonvulsant therapy should be initiated subsequent to the initial late onset post-stroke seizure. [102] Gabapentin, administered at a daily dosage of 900 – 1800 mg, is one of the advocated pharmacological agents for treating adults following the first late-onset convulsion[102]. Monitoring patients over a span of 30 months, the investigators noted a recurrence rate of approximately 18% within the cohort. Adverse effects necessitating cessation of the medication were documented in 3% of the subjects[102]. Oros et al. elucidated that recurrent epileptic paroxysms afflicted 27% of individuals with acute ischemic stroke (AIS) who were administered anticonvulsants within 1 – year post initial post – stroke seizure, whereas nearly 54% of those who abstained from antiepileptic intervention experienced repeated convulsive episodes[103]. In the majority of cases, post-stroke epilepsy is efficaciously managed with mono – therapeutic regimens[104]. Given that the convulsions in post – stroke epilepsy are inherently focal, the initial pharmacological intervention in European adults often involves carbamazepine and gabapentin, whereas in the United States, the preferred first – line agents are phenytoin and gabapentin[103,105]. Nevertheless, in Japanese population afflicted with post-stroke epilepsy, the dispensation of valproic acid as the foremost pharmacological remedy is more ubiquitous, owing to the fact that the second – generation anticonvulsant agents remain unratified within this jurisdiction[100,106]. In the stochastic noncontrolled trial by Gilard et al., juxtaposing the potency and adverse reactions of lamotrigine and carbamazepine, the former exhibited superior efficacy, with subjects administered lamotrigine reporting a diminished incidence of adverse reactions[107]. However, on comparing the efficacy between levetiracetam and carbamazepine, it did not elucidate any discernible pre-eminence of either pharmacological agent, although levetiracetam demonstrated enhanced tolerability[108]. As per Billinghurst et al., convulsive episodes in pediatric AIS cases were predominantly managed with levetiracetam, phenobarbital and phenytoin (62%, 46% and 8%, correspondingly). Approximately a quarter of the cohort necessitated polytherapy with multiple anticonvulsants at the point of discharge[109]. The prognostication in adult – onset post – stroke epilepsy appears markedly propitious. Stephen et al., surveyed a cohort of individuals afflicted with post – stroke epilepsy over a biennial duration, the majority necessitated merely a singular AED, and by the culmination of the second annum of scrutiny, up to 67% of the cohort attained seizure abeyance[110].

Conclusion

Post – stroke seizures (PSS) constitute prevalent sequelae of apoplexy. It is crucial to methodically scrutinize, assess, categorize, and administer interventions, differentiating them from anomalous movement disorders, syncopal events and psychogenic non - epileptic seizures (PNES) predicated based on the semiology. A meticulous approach and identification of etiological factors beyond cerebrovascular structural aberrations that may precipitate acute symptomatic seizures are essential. Upon confirmation of a post – stroke seizure, we can adeptly manage patients, enhance their prognostic outlook by ascertaining whether the episode is early or late, and devise a therapeutic regimen tailored to their specific

pathophysiological state. This elucidates the intricate etiology of post – stroke epilepsy and its prognostication. Consequently, the greater the erudition concerning post-stroke epilepsy, the more sophisticated, exacting, and potentially bespoke interventions stand to be actualized.

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