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Sajid Hameed

Aga Khan University, Karachi

Haris Hakeem

Aga Khan University, Karachi

Mohammad Wasay

Aga Khan University, Karachi

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POST-STROKE SEIZURES: A CLINICALLY ORIENTED ANALYSIS

Sajid Hameed,¹ Haris Hakeem,¹ Mohammad Wasay¹

¹Section of Neurology, Aga Khan University Hospital

Correspondence to: Haris Hakeem, (dr.harishakeem@gmail.com)

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ABSTRACT:

Stroke is an important cause of secondary epilepsy, especially in the elderly. Not only does this impact morbidity and mortality in an adverse way, it also prolongs the hospitalization. Various risk factors have been described in literature that increase the risk of seizures in a patient with stroke. Post stroke seizures fall on a spectrum of acute symptomatic and unprovoked seizures with varying pathophysiology and risk of subsequent development of epilepsy. Hence, the treatment approaches are also different. However, randomized controlled trials are lacking to guide monitoring and management strategies in post stroke seizures and the approaches remain individualized to an extent. This clinically oriented analysis discusses these important issues in the light of published literature and gives directions on future areas of research.

INTRODUCTION:

Stroke is the most common identified cause of secondary epilepsy in elderly patients^[1-2]. In 1864, Hugling Jackson first observed an association of seizures in patients suffering from stroke and in 1885, William Gowers first described “post-hemiplegic epilepsy”^[3]. Post-stroke seizures (PSS) not only increase mortality and morbidity in patients with stroke but these patients also have increased disability at discharge and have an extended hospital stay as compared to stroke patients without PSS^[4]. In the last few decades, multiple studies have been done to underline the association of stroke and the relation of multiple risk factors with the development of PSS but a lot of ground is yet to be covered.

MATERIALS AND METHODS:

An online literature search was conducted through the Medline database and Cochrane library (PubMed/Cochrane library). We used the following search keywords terms: “poststroke epilepsy”, OR “poststroke seizure”, OR “epilepsy after stroke”, OR “seizure after stroke”. We included the articles that were published in English, contain human specimens, and carried out in adults above 18 years from January 2000 to June 2019. Our search retrieved a total of 897 results, with 885 in PubMed and 12 reviews in the Cochrane library. 842 results out of 897 were excluded due to duplicate

results, unrelated title/abstract, short commentaries, and inaccessible full articles. Finally, 25 full-text articles were included in this review. We also examined the references of the included articles and four additional articles were included in this review.

CLASSIFICATION & PATHOPHYSIOLOGY

Post-stroke seizures are divided into two main types, the acute symptomatic seizure (ASS) and unprovoked seizure (US). This distinction is important due to their different presumed pathophysiology and long-term risk of seizure recurrence^[5], which is approximately 20% after a single ASS and 71% after the first US^[6]. These types are also referred to in the literature as early-onset and late-onset PSS, respectively, but the former terms are preferred and will be used in this review.

ASS is defined as a seizure occurrence within seven days of stroke^[7-8]. However, in different studies, this time duration defined for ASS varies, ranging from 24 hours to 28 days^[7]. ASS is presumed to occur as a result of acute transient biochemical cellular changes secondary to neuronal ischemia. These changes include ion channel dysfunction, intracellular calcium accumulation, glutamate excitotoxicity, and disruption of the blood-brain barrier^[9]. The surrounding ischemic penumbra, being an electrically irritable tissue, also functions as an epileptogenic area^[3].

US is defined as a seizure occurrence after seven days of

stroke^[7]. The probability of recurrence of seizures after a single US is at least 60% over the next 10 years (similar to the general recurrence risk after two unprovoked seizures), therefore, the post-stroke patients with US can be labeled as having post-seizure epilepsy (PSE) even after one US, as defined by the International League Against Epilepsy^[7]. The same is not true for ASS, which has a lower risk of seizure recurrence and is not associated with an adverse clinical outcome after stroke^[10]. The pathophysiology of US is presumed to be due to chronic inflammation, neurodegeneration, and gliosis with the associated remodeling of synaptic networks. These changes result in neuronal hyperexcitability, neuronal hypersynchrony, and resultant increased risk of seizures^[9].

EPIDEMIOLOGY

Stroke is considered the most common identified cause of secondary epilepsy. One large epidemiological study identified stroke as the main etiology in 11% of the patients with secondary epilepsy^[11]. The incidence of PSS increases with increased follow-up duration after stroke. Graham et al. followed 3310 patients in the United Kingdom with the first stroke and calculated an estimated cumulative risk of PSS of 1.5% at 3-months, which increased to 12.4% at 10-years^[1]. Another large prospective study in Taiwan reported that 2.6% cases (109 out of 4126) developed epilepsy during the 5-year post-stroke follow up. The incidence was highest for the patients having multiple subtypes of strokes (7.7%) and was the lowest for patients with ischemic stroke alone (1.6%)^[12].

The incidence of ASS and US varies among different studies, partly due to heterogeneous study designs, different defined durations of ASS and US, and variable follow-up periods. The incidence of ASS has been reported from 2% to 33% but consistently, more than half of the ASS occur within the first 24 hours after stroke^[9,13,14]. Some studies report a higher incidence of ASS in young male patients, while other studies show no difference between age and gender^[3,10]. The incidence of US varies from 3% to 67%^[9,13,14]. US is more common between 6 and 12 months after stroke [9], nonetheless, US may still develop after 10 years post-stroke^[3].

Risk factors

Multiple studies related to PSS have stratified data to identify independent risk factors that predict seizure occurrence after stroke. Although numbers vary among studies due to different methodologies and follow-up periods, some risk factors have been repetitively identified in most of the studies that include hemorrhagic stroke type, cortical involvement, anterior circulation

infarct, young age and seizure in the early period after stroke. Despite an increased risk of seizures in these groups, prophylactic treatment with anti-epileptic drugs is not recommended. This will be further discussed in the next section.

Stroke type

Hemorrhagic strokes are reported to have a higher incidence of PSS as compared to ischemic strokes. A large 5-year follow-up study in Taiwan reported post-stroke epilepsy in 4.3% of patients with hemorrhagic stroke, 4.2% of patients with subarachnoid hemorrhage and only 1.6% of patients with ischemic stroke. However, the incidence was the highest (7.7%) for patients with strokes of multiple subtypes – mostly hemorrhagic as well as ischemic stroke^[12]. Ferlazzo et al. reported a two-fold increased risk of seizures with hemorrhagic strokes (OR 2.41, 95% CI 1.57–3.69, $p < 0.001$) in their meta-analysis^[15]. An increased risk for PSS was also reported among patients with subarachnoid hemorrhage and infarctions with the hemorrhagic conversion. Hemosiderin deposits increasing cerebral epileptogenicity, by causing overproduction of reactive oxygen species and resultant oxidative stress, is presumed to be the cause of increased PSS in these patients, although the exact cause remains largely unknown^[16].

Among ischemic strokes, multiple studies found an increased association of ASS with embolic infarcts as compared to thrombotic infarcts, but the same results are not replicated in other studies and this association is still inconclusive^[3].

Stroke Location:

Strokes with cortical location are more frequently associated with PSS^[3,15]. It increases the relative risk of PSS by almost four times (OR 3.71, $p < 0.001$) as compared to subcortical strokes^[15]. Cortical irritation is presumed to be the cause of higher epileptogenicity of cortical strokes^[3]. Lacunar strokes are also rarely associated with seizures^[17].

STROKE SIZE:

Stroke size is considered one of the risk factors for post-stroke epilepsy, as the notion goes, the larger the size of the stroke, the greater the risk of future seizures. A 10 mm increase in stroke size on CT scan increases the relative risk of PSS by 16% within 7 years^[18]. Large strokes involving multiple lobes of the brain are associated with an increased risk of PSS than the strokes involving single lobe. In the Oxfordshire Community Stroke Project, PSS was seen in 11% of patients with

total anterior circulation infarcts as compared to only 1% of patients with lacunar strokes [17]. In another study, 56% of the patients developed PSS after malignant middle cerebral artery (MCA) infarcts and decompressive hemicraniectomy [2]. However, a few studies have also failed to establish a significant association between stroke size and seizures [13].

STROKE SEVERITY:

Most studies agree that severe neurological deficits at the stroke presentation are associated with an increased risk of PSS. Stroke severity is measured by different scales including the Scandinavian Stroke Scale (SSS) [18] and National Institute of Health Stroke Scale (NIHSS) [1,9]. A 10-point decrease in the SSS score increases the risk of PSS by more than 25% [18]. This is in part presumed that severe strokes involve multiple lobes of the brain and are mostly cortical in location.

ACUTE ASYMPTOMATIC SEIZURES:

Acute asymptomatic seizures or early seizures are independent risk factors and increase the risk of PSS by more than four times. (OR 4.43, $p < 0.001$) [15]. The same 4-fold increase in PSS after ASS was also reported by Kammergaard in the Copenhagen stroke study [18]. Another study reported that after a single ASS, the 10-year risk of US reaches 30% [6].

AGE:

In the Copenhagen stroke study, younger age was associated with an increased risk of PSS. A 65% increase in the risk of PSS is reported with a 10-year decrease in age at stroke onset [18] but similar results were not reported in other studies [15,19]. The higher incidence reported in some studies may be due to increased survival after a stroke rather than an independent risk factor. Some studies have also reported that younger individuals tend to have increased number of larger strokes due to large artery occlusion as compared to many small artery strokes in elderly, which may also be one of the reasons for increased risk of PSS in the younger population.

GENDER:

Although stroke is more common in the male gender, a significant difference in PSS was not reported between male and female gender (OR 0.943 for the female sex, 95% CI 0.79–1.13, $p = 0.52$) [3,15].

TISSUE PLASMINOGEN ACTIVATOR:

The association of tissue plasminogen activator (tPA)

treatment for ischemic stroke with PSS is not well studied. Three studies have reported an increased incidence of PSS with tPA treatment [20-22], while others have found no association [23]. Naylor et al. reported PSS in 21 out of 363 patients (5.8%) treated with IV tPA (OR 3.7, $p < 0.0001$), while 12 out of 93 patients (12.9%) with intraarterial tPA developed PSS (OR 5.5, $p < 0.0001$). These numbers were significantly higher as compared to the patients who were given standard care without reperfusion therapy (2%) [22].

OTHERS:

Dementia is considered a significant risk factor for US (OR=4.66), which is presumed to be due to glutamate pathway dysfunction in these patients [24]. Antidepressants, antipsychotic or anxiolytic medications have also been reported to increase the risk of PSS in some studies [4] but more well-controlled studies are needed to establish an association of these medicines with PSS. For unknown reasons, urinary incontinence at stroke presentation is also associated with PSS [1]. In the majority of studies, underlying cardiovascular comorbidities, for instance, hypertension, diabetes, hyperlipidemia, and atrial fibrillation, did not increase the risk of PSS [25]. However, the use of statins decreased the risk of epilepsy in some studies [26].

CAVE SCORE:

Given the aforementioned risk factors, Haapaniemi et al. proposed a scoring system to predict the risk of US in patients with intracerebral hemorrhage. It carries one point each for cortical involvement, age < 65 years, the volume of hemorrhage > 10 ml, and early seizure, with scores ranging from 0 to 4. The risk of US was calculated as 0.6%, 3.6%, 9.8%, 34.8% and 46.2% for CAVE scores 0–4, respectively, as shown in Table 1 [27].

Criteria	Points
Cortical involvement	1
Age < 65 years	1
Volume > 10 ml	1
Early Seizure (Acute symptomatic seizure)	1
Risk of US:	
0 point: 0.6%	
1 point: 3.6%	
2 points: 9.8%	
3 points: 34.8%	
4 points: 46.2%	

EEG IN POSTSTROKE SEIZURES:

The detection of seizures in post stroke setting may not be straight forward. [28] Patients may not always have clinically obvious seizures and subtle manifestations such as intermittent gaze deviation or nystagmus, mild facial twitching or focal positive sensory symptoms. In addition, patients may present with intermittent altered

mentation resembling delirium. These cases with sub-clinical seizures can only be definitively diagnosed by EEG monitoring.^[9] The duration of EEG monitoring may vary from regular (20-45 minutes) or extended (1-2 hours) to continuous long-term (up to 24 hours or longer). Although some studies have shown long-term EEG monitoring to be superior in detection of non-convulsive seizures, there are no definitive guidelines as of now, regarding the optimum duration of EEG monitoring in post-stroke patients and the practices are variable depending on resources and remain institution based.^[28] The various EEG abnormalities that may be encountered in this setting can be broadly divided in to: (1) non-specific abnormalities (focal or diffuse slowing, asymmetric attenuation of faster frequency activities, including sleep specific activity);^[29] (2) interictal epileptiform abnormalities such as spike and sharp transients and intermittent periodic discharges (lateralized, bilateral independent or generalized), all generally indicating increased probability of having seizures; and (3) ictal abnormalities (electrographic seizures).^[9]

TREATMENT:

Treatment of PSS is generally individualized based on clinician's experience and the patient's condition due to the lack of multiple randomized controlled trials (RCTs) to guide therapeutic decisions. The European Stroke Organization (ESO) has suggested certain recommendations to help in the prevention and management of PSS, based on several observational studies and few available RCTs [5]. The management of PSS can be divided into two main categories; (i) preventive or prophylactic treatment and (ii) symptomatic treatment.

PRIMARY PROPHYLAXIS FOR ACUTE SYMPTOMATIC SEIZURE

Primary prophylactic treatment for ASS is not recommended^[5,9] because the general risk of developing ASS in the patients with a stroke is only about 5%, which is very low^[5]. The presence of large volume, cortical intracerebral hemorrhage increases the risk of ASS to as much as 35% and a few clinicians may start anti-epileptic drugs (AEDs) in these selected cases, however, the risk of ASS is still not significant enough to recommend primary prophylaxis. Temporary primary prophylaxis with AEDs after stroke does not decrease the future risk of US and does not affect the mortality rates^[30]. On the other hand, AEDs are loaded with significant side effects. It is also unclear when to stop the AEDs once they are started prophylactically.

TREATMENT FOR ACUTE SYMPTOMATIC SEIZURE

Treatment with AEDs after a single ASS is not recommended^[5]. The general risk of seizure recurrence after a single ASS is only 20%, which is almost the same as for the single US in a general population. Many neurologists still prefer to initiate AEDs to avoid complications in the acute stroke setting, especially if a patient had multiple ASS (within 24 hours) or had intracerebral hemorrhage^[9]. If AEDs are started after a single ASS, it is recommended that the drugs should be withdrawn after four weeks of stroke [5,9].

PRIMARY PROPHYLAXIS FOR UNPROVOKED SEIZURE

The use of AEDs for the primary prophylaxis for US is not recommended by ESO^[5]. The general risk of first US in a patient with stroke is only 10%. The risk of US increases to 46.2% in a patient with intracerebral hemorrhage having a CAVE score of 4 (i.e. cortical involvement, age <65 years, volume >10 ml and ASS)^[27]. In these patients, primary prophylaxis for US with AEDs is optional and may be individualized. After the initiation of AEDs, another important concern is the time to stop the AEDs for which the answer is still unclear.

TREATMENT FOR UNPROVOKED SEIZURE

In previous studies, the single US after stroke did not constitute post-stroke epilepsy and AEDs were only started after two or more US^[9]. The current literature suggests that a single US increases the 10-year risk of seizure recurrence by > 70%^[6], and can be labeled as post-stroke epilepsy after single US^[7], therefore, the initiation of AEDs after the first US is recommended^[5]. Regarding the choice of AEDs in PSS, RCTs are not available to recommend one AED over another. Generally, an AED is selected based on the patient's general condition as well as safety profile and adverse effects related to AED. Carbamazepine and phenytoin are traditionally used in the treatment of PSS [16] but these AEDs induce hepatic enzymes, have known interactions with multiple other drugs, and greater side effects. The secondary stroke prophylaxis may also be affected since carbamazepine and phenytoin have interactions with the newer anticoagulants including apixaban and dabigatran^[26]. Lamotrigene and levetiracetam are the other options to treat PSS with better tolerability and less drug-drug interactions. There was no significant difference in efficacy when levetiracetam and lamotrigene were compared with carbamazepine in two separate studies^[31,32]. Once started, the decision to discontinue AEDs is individualized. AEDs may be continued permanently as the risk of seizure recurrence is high after the withdrawal of drugs^[5].

FUTURE DIRECTIONS

Despite the advancements made in our understanding of post-stroke seizures over the years, many questions still remain elusive. These include: (1) An association of PSS with the newer reperfusion therapies. (2) Choice of AED in the management of PSS. (3) Morbidity and mortality benefits of long-term treatment of unprovoked seizures with AEDs. Large scale well-controlled randomized trials are needed to further expand our knowledge and recommend practice guidelines for better patient care with PSS

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Author's contribution:

Sajid Hameed; concept, data collection, data analysis, manuscript writing, manuscript review

Haris Hakeem; data collection, data analysis, manuscript writing, manuscript review

Mohammad Wasay; concept, data analysis, manuscript writing, manuscript review