CNS Spectrums (2020), **25**, 101–113. © Cambridge University Press 2019
doi:10.1017/S1092852919000804

REVIEW ARTICLE

Early seizures after ischemic stroke: focus on thrombolysis

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Introduction. Stroke is a significant underlying cause of epilepsy. Seizures due to ischemic stroke (IS) are generally categorized into early seizures (ESs) and late seizures (LSs). Seizures in thrombolysis situations may raise the possibility of other etiology than IS.

Aim. We overtook a systematic review focusing on the pathogenesis, prevalence, risk factors, detection, management, and clinical outcome of ESs in IS and in stroke/thrombolysis situations. We also collected articles focusing on the association of recombinant tissue-type plasminogen activator (rt-PA) treatment and epileptic seizures.

Results. We have identified 37 studies with 36,775 participants. ES rate was 3.8% overall in patients with IS with geographical differences. Cortical involvement, severe stroke, hemorrhagic transformation, age (<65 years), large lesion, and atrial fibrillation were the most important risk factors. Sixty-one percent of ESs were partial and 39% were general. Status epilepticus (SE) occurred in 16.3%. 73.6% had an onset within 24 h and 40% may present at the onset of stroke syndrome. Based on EEG findings seizure-like activity could be detected only in approximately 18% of ES patients. MRI diffusion-weighted imaging and multimodal brain imaging may help in the differentiation of ischemia vs. seizure. There are no specific recommendations with regard to the treatment of ES.

Conclusion. ESs are rare complications of acute stroke with substantial burden. A significant proportion can be presented at the onset of stroke requiring an extensive diagnostic workup.

Received 6 June 2018; Accepted 7 February 2019

Key words: Emergency service, imaging, ischemic stroke, seizure, stroke, thrombolysis, treatment.

Introduction

Stroke is the leading cause of disability and one of the leading causes of death. It also accounts for up to 11% of epilepsy.[1] Population-based data have shown that stroke is the underlying cause of epilepsy in older adults in more than 30%.[2]

Seizures due to ischemic stroke (IS) are generally categorized into early seizures (ESs) (≤1–4 weeks) and late seizures (LSs) (≥1–4 weeks) based on different studies, but no consensus exists; however, ESs were defined by the International League Against Epilepsy as those occurring within 7 days of stroke onset.[3,4]

Tissue plasminogen activator (tPA) thrombolysis remains the gold standard treatment for IS within a limited window (~4–5 h in most countries in Europe).[5] Stroke mimics (including postseizure palsies) can account for approximately one of five clinically diagnosed acute strokes and the rate of stroke mimics (ictal or postictal paralysis, migraine, hysteria, hypoxic hemiplegia, and hypoglycemia) who are thrombolyzed can be as high as 17%.[6] Based on recent trials, single-center and case-control studies stroke mimics are most likely identified as seizures or conversion disorder.[7,8]

On the other hand, the recent AHA guideline states that seizure at onset with postictal residual neurological impairments is a relative exclusion criterion based on the

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This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

All authors equally contributed to the manuscript including study concept and design, collection of data, analysis and interpretation of data, writing of manuscript, and critical revision of manuscript.

findings of low-quality evidence (case series), suggesting that these residual deficits are attributable to ischemia rather than the postictal state.[9]

Moreover, experimental studies suggested that recombinant tissue-type plasminogen activator (rt-PA) may play a role in the development of seizures/epilepsy. In rodent models, t-PA expression was increased after seizures and mediated kainic acid-induced seizure propagation, whereas t-PA/−/ mice are resistant to chemoconvulsant-induced seizures.[10] Recent clinical studies showed its possible association with ESs.[11]

Multimodal patient imaging (perfusion computer tomograph (CT) and magnetic resonance imaging (MRI) techniques) are important parts of acute stroke imaging to delineate the infarct from ischemic penumbra in specific situations such as stroke of unknown time of onset (SUTO) or in endovascular intervention with extended time window.[12,13] Perfusion techniques play a vital role in diagnosing stroke mimics in stroke/thrombolysis pathway when the etiology is doubtful or in patients with SUTO .[14]

The aim of our review was to summarize the findings of different studies focusing on the pathogenesis, prevalence, risk factors, detection, management, and clinical outcome of ESs in IS and in stroke/thrombolysis situations. We also collected articles focusing on the association of rt-PA treatment and epileptic seizures.

We searched PubMed, MEDLINE, and the Cochrane Library restricted to English language publications to April, 2017. We used these search items in the following combinations: stroke, IS, seizure, ES, poststroke epilepsy (PSE), thrombolysis, rt-PA, alteplase, imaging, perfusion imaging, CT, MRI, electroencephalogram (EEG), outcome, and mortality. After reviewing the abstracts, we obtained and reviewed the full text and reference lists of relevant articles.

Pathogenesis of Early Ischemic Seizures

Mechanisms of early and late poststroke seizures are relatively poorly studied, mainly due to limited developments in animal modeling.[15] PSE has different pathophysiologic mechanisms based on these experimental data; transient cellular biochemical dysfunctions play an important role in the development of ESs, while gliotic scarring with persistent changes can initiate LSs.[16]

Acute arterial occlusion and hypoperfusion lead to the loss of neurovascular unit integrity. Albumin enters the brain due to increased vessel wall permeability, binds directly to the astrocytes, and activates transforming growth factor beta (TGFβ). The activation of TGFβ signalling pathway leads to extracellular accumulation of potassium and glutamate due to reduced astrocytal uptake, with consequent hyperexcitability and low seizure threshold.[17] Glutamate is a major excitotoxic neurotransmitter and acts through various receptors including alpha-amino3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainate, and N-methyl-D-aspartate (NMDA). The activation of these receptors results in intracellular inflow of calcium and sodium lowering the seizure threshold for depolarization and leading to neuronal damage and death.[17,18] Furthermore, the excitatory neurotransmitter glutamate (Glu) and the inhibitory neurotransmitter γ-aminobutyric acid (GABA) have a close inverse relationship.[18]

Extravasated thrombin can bind the astrocytes to protease-activated receptor-1.[15-17] Activated microglial cells and astrocytes release proinflammatory cytokines such as interleukin (IL)-1b, high-mobility group box 1 (HMGB1), tumor necrosis factor a (TNFa), IL-6, and IL-1b, worsening vessel injury and promoting PSE.[15-17]

In their clinical study, Xie et al. aimed to identify early predictors of PSE by measuring changes in blood levels of GABA, Glu, and calcium (Ca^{2+}). They showed that patients with poststroke seizures had higher glutamate and lower calcium in their plasma compared to seizure-free cerebrovascular patients underlying the possible clinical importance of these molecules.[18]

ESs after Stroke

Included studies

We have identified 37 studies with 36,775 participants[11,19-53] (Table 1). Thirteen retrospective, single-center (15,190 patients), 15 prospective, single-center (9593 patients), 5 prospective, observational, population-based (7710 patients), and 4 prospective, multicenter (4282 patients) studies were identified (Table 1).

Cut-off values for the occurrence of ESs were different, from 24 h to 30 days. Twenty-one studies applied 1 week, 13 studies applied 2 weeks, 2 studies applied 30 days, and 1 study applied 24 h cut-off point.

Fourteen studies reported ES rates in IS, and the remaining studies also included patients with hemorrhagic stroke (HS)/subarachnoid hemorrhage (SAH) or with cerebral venous thrombosis (CVT) (Table 1).

Early seizure rates

ES rate was 1633/36,775 (4.4%) in the whole population. These rates were 3.4% in retrospective, single-center (519/15,190), 6.2% in prospective, single-center (597/9593), 3.5% in prospective, observational, population-based (272/7710), and 5.7% in multicenter studies (245/4282). As vast majority of these studies included patients with hemorrhagic stroke syndromes (HS, SAH) or CVT, we also calculated ES rates in IS (if reported).

ES rate was 3.8% (1012/26,409) overall in patients with IS; 3% (303/10,106) in retrospective, single-center, 5.4% (376/6991) in prospective, one-center, 2.5%

https://doi.org/10.1017/S1092852919000804 Published online by Cambridge University Press

TABLE 1. Included studies

Study	Study design	Patient number	Population	ES definition	ES rate
Kim et al.[19]	Retrospective, single-center	3792	IS	<1 week	48/3792 (1.3%)
Bryndziar et al.[20]	Retrospective, single-center	489	IS	<2 weeks	14/489 (2.8%)
Mohamed and Kissani[21]	Retrospective, single-center	352	IS	<1 week	47/352 (13.3%)
Wang et al.[22]	Retrospective, multicenter	2474	IS, HS, SAH	<2 weeks	123/2474 overall (5%) *(not reported in IS)*
Arntz et al.[23]	Prospective, single-center	697	TIA, IS, HS	<1 week	25/697 overall (3.6%) *20/425 in IS (4.7%)*
Jung et al.[24]	Prospective, single-center	805	IS (endovascular treatment)	<24 h	26/805 (3.2%)
Alberti et al.[25]	Prospective, single-center	638	IS, HS	<1 week	31/638 (4.8%) *26/543 in IS (4.8%)*
Khealani et al.[26]	Retrospective, single-center	1548	IS, HS	<2 weeks	117/1548 (8%) 97/1117 in IS (8.6%)
Cordonnier et al.[27]	Prospective, single-center	169	IS	<1 week	9/169 (5.3%)
Chen et al.[28]	Retrospective, single-center	348	IS	<1 week	5/348 (1.4%)
Hundozi et al.[29]	Retrospective, single-center	1073	IS, HS, SAH, CVT	<2 weeks	44/1073 (4.1%) *33/794 in IS (4.1%)*
Conrad et al.[30]	Retrospective, single-center	421	TIA, IS, HS, CVT	<1 week	23/421 (5.5%) *12/307 in IS (3.9%)*
Hamidou et al.[31]	Prospective, population-based observational study	4358	IS, HS, SAH	<2 weeks	134/4358 (3.1%) *86/3607 in IS (2.4%)*
Couillard et al.[32]	Retrospective, single-center	400	IS (treated with alteplase)	<1 week	16/400
Strzelczyk et al.[33]	Prospective, single-center	264	IS, HS	<2 weeks	12/264 (4.5%) not reported in IS
De Reuck and Van Maele[34]	Retrospective single-center	1076	IS	<2 weeks	39/1076 (3.6%)
Stefanidou et al.[35]	Prospective, population-based observational study	469	IS	<30 days	12/469 (2.6%)
Cheung et al.[36]	Retrospective, single-center	994	IS, HS, SAH	<30 days	16/994 (1.6%) *not reported in IS*
Kammersgaard et al.[37]	Prospective, population-based observational study	1197	IS, HS	<2 weeks	50/1197 (4.1%) *not reported in IS*
Labovitz et al.[38]	Prospective, population-based epidemiologic study	904	IS, HS, SAH	<1 week	37/904 (4.1%) *22/704 in IS (3.1%)*
Lamy et al.[39]	Prospective, multicentre	581	IS	<1 week	14/581 (2.4%)
Cordonnier et al.[40]	Prospective, single-center	202	IS, HS	<1 week	11/202 (5.4%) *8/169 in IS (4.7%)*
Bladin et al.[41]	Prospective, multicentre	1897	IS, HS	<2 weeks	168/1897 (8.8%) *140/1632 in IS (8.6%)*
Serafini et al.[42]	Prospective, population-based observational study	782	IS, HS, SAH	<1 week	39/782 (5%) *17/620 in IS (2.7%)*
Dewan and Rana[43]	Prospective, single-center	100	IS	<2 weeks	12/100 (12%)
Panitchote and Tiamkao[44]	Retrospective, single-center	372	IS, HS, CVT	<2 weeks	35/372 (9.4%) *not reported in IS*
Goswami et al.[45]	Prospective, single-center	441	IS, HS	<1 week	79/441 (17.9%) *28/224 in IS (12.5%)*
Aiwansoba and Chukwuyem[46]	Prospective, single-center	251	IS, HS	<1 week	25/251 (10%) *not reported in IS*
Pezzini et al.[47]	Prospective, single-center	516	IS, HS	< 1 week	20/516 (3.9%) *12/436 in IS (2.7%)*
Procaccianti et al.[48]	Prospective, single-center	2053	IS, HS	<1 week	66/2053 (3.2%) *58/1742 in IS (3.3%)*
Mecarelli et al.[49]	Prospective, single-center	232	IS, HS	<1 week	15/232 (6.4%) *not reported in IS*
Beghi et al.[50]	Prospective, multicenter	714	IS, HS	<1 week	45/714 (6.3%) *24/609 in IS (3.9%)*
Misirli et al.[51]	Prospective, single-center	1880	IS, HS	< 2 weeks	200/1880 (10.6%) 138/1302 in IS (10.6%)
Dhanuka et al.[52]	Prospective, single-center	269	IS, HS	<1 week	27/269 (10%) *not reported in IS*
Leys et al.[53]	Prospective, multicenter	1090	IS (treated with alteplase)	<1 week	18/1090 (1.6%)
De Reuck and Van Maele[54]	Retrospective, single-center	180	IS	<2 weeks	3/180 (1.6%)
Alvarez et al.[11]	Retrospective, single-center	2327	IS (treated with alteplase)	<1 week	28/2327 (1.2%)

CVT, cerebral venous thrombosis; HS, hemorrhagic stroke; IS, ischemic stroke; SAH, subarachnoid hemorrhage; TIA, transient ischemic attack.

https://doi.org/10.1017/S1092852919000804 Published online by Cambridge University Press

(137/5400) in prospective, population-based, observational, and 4.3% (196/3912) in multicenter studies (Table 1).

ES rates were 3.5% (104/2959) in 5 studies from Northern America overall (84/2487, 3.3% in IS), 3.4% (304/8808) in 4 studies from the Far East (97/1117, 8.7% in IS), 9.5% in 4 studies from South Asia (40/324, 12.3% in IS), 10.6% (200/1880) in 1 study published from the Near East (Turkey) (138/1302, 10.6% in IS), 12% (72/603) in 2 studies from Africa (47/352, 13% in IS), 3.8% (795/20,575) in 20 studies (including all multicenter studies and 3 prospective, observational population-based studies) from Europe (532/16,720, 3.2% in IS).

Risk factors of early seizures

Cortical involvement (especially anterior) (13 studies), severe stroke (10 studies), hemorrhagic transformation (6 studies), age <65 (4 studies), large lesion (3 studies), and atrial fibrillation (3 studies) were the most important risk factors of ESs (Table 3). Hemorrhagic stroke syndromes (both HS and SAH) were also important predictors.[22,30,41,44,45,50]

Metabolic disturbances such as elevated blood glucose or low sodium levels can also precipitate seizures.[22,30,42,48] Low blood pressure and normal lipid levels seem to have protective effect.[29,44,53] The other risk factors were low ASPECTS score, alcoholism, previous stroke, male gender, and impaired consciousness[28,31,36,45,54] (Table 2).

Only 13 studies reported risk factors of late/recurrent seizures and epilepsy.[19,22,23,28,37,39–42,52–54] Severe and cortical strokes were the most important risk factors; ESs were associated with recurrent seizures/epilepsy in two studies[37,39] (Table 2).

The impact on clinical outcome is controversial: eight studies reported ESs as predictors of worse clinical outcome, while seven studies showed neutral effect[20–23,31,32,38,41–45,47,50,52,53] (Table 2).

Early seizure type

Twenty studies reported clinical data with regard to ES type.[19,20,22–24,27,30,32,35,36,38–40,46–48,50,51,53,54] Based on their results, 63.8% (725/1137) seizures were partial and 35.2% (400/1137) were general at onset. Twelve seizures cannot be classified due to lack of adequate clinical data in five from the above-mentioned studies (12/1137, 1%).[23,27,30,38,40] Status epilepticus (SE) occurred in 22.9% (130/567)[19–21,27,30,36,38–40,42,47–49,52,54] (Table 3).

Partial seizures were simplex partial in 63.8% (245/384) and complex partial in 36.2% (139/245) based on the results of six studies[22,32,36,38,48,54] (Table 3).

59.7% (273/457) of ESs occurred within 24 h,[19,20,35,38–41,48–50,52] and 39.6% was presented at the onset of stroke (19/48) based on the results of two studies.[38,40]

As vast majority of these studies included patients with different stroke syndromes (IS, HS, SAH, and CVT), we also calculated ES type rates in IS (if reported).

Only six studies reported data on seizure type in IS.[19,27,32,35,39,53] Sixty-one percent were partial (79/130) and 39% were general (47/130), and four patients had inadequate clinical data.[27,32] Partial seizures were simplex partial in 55.6% (5/9) and complex partial in 44.4% (4/9) based on the result of only one study.[32] SE occurred in 16.3% (32/196).[19,20,27,36,38–40,47,52] 73.6% (112/152) had an onset within 24 h.[19,20,35,38,39,52] Due to the lack of clinical data, we could not calculate seizure rate at stroke onset.

EEG findings

Eight studies reported EEG findings in poststroke seizures and the data of four additional studies were also included.[19,20,22,26,30,50,52,54–58] 11.9% (88/739) had normal EEG, 49.3% (389/739) had diffuse/focal slowing, and 35% (259/739) had epileptiform discharge/periodic lateralized epileptiform discharge (PLED). Data of three patients were missing (0.3%).[20]

EEG findings in IS/ES were properly reported in three studies.[55–57] Based on their results, 19.8% (19/96) had normal EEG, diffuse slowing can be detected in 24% (23/96), focal slowing could be found in 37.5% (36/96), and 18.8% (18/96) had PLED/epileptiform discharge (Table 4).

Brain imaging

Plain CT is the cornerstone of CT imaging to rule out hemorrhage; however, it has very limited role in the differentiation of stroke mimics.[59]

CT angiography (CTA) can be helpful to pick up large artery occlusion (but not in other conditions, for example, lacunar stroke syndromes), and only one study showed its contribution to decision making for thrombolysis.[60]

We found 20 studies focusing on MRI diffusion-weighted imaging (DWI) changes in seizure patients.[61–80] Five case reports, 1 case series, and 16 single-center studies cover overall 355 patients (Table 5). Based on their results, most often DWI or ADC abnormalities could be detected in the hippocampus, thalamic/pulvinar region, and in the corpus callosum in the vast majority of the studies (Table 5). DWI changes may occur in various cortical and cerebellar locations helping in the identification of epileptic foci (for example, aphasic seizure seemed to be associated with temporoparietal DWI changes based on the results of two case reports).[65,72] Multiple DWI changes could be associated with longer and recurrent seizures in IS patients as reported by Kumral et al.[71]

https://doi.org/10.1017/S1092852919000804 Published online by Cambridge University Press

TABLE 2. Risk factors of early and LSs

Study	Risk factors of ESs	Risk factors of LSs/epilepsy	Other findings
Kim et al.[19]	Not reported	Male gender, atrial fibrillation, cortical involvement, high NIHSS scale	Patients with LSs had a greater chance of developing epilepsy later
Bryndziar et al.[20]	Independent predictors were not identified	Not reported	Worse outcome in patients with poststroke seizure
Mohamed and Kissani[21]	Initial stroke severity, large IS, cortical involvement, hemorrhagic transformation	Not reported	ES seems to be associated with a worse outcome after acute stroke
Wang et al.[22]	Large lesion, SAH, hyponatremia, cortical involvement	Cortical involvement, large lesion	–
Arntz et al.[23]	Not reported	High NIHSS	Patients with LSs had a greater chance of developing epilepsy later
Jung et al.[24]	Asymptomatic ICH, younger age, high NIHSS	Not reported	ES was independent predictor of worse outcome
Alberti et al.[25]	Hemorrhagic transformation	Not reported	ES did not influence mortality/disability
Khealani et al.[26]	Not reported	Not reported	Early sepsis is associated with seizure recurrence
Cordonnier et al.[27]	Not reported	Not reported	Epileptic seizures were independent predictors of new-onset dementia
Chen et al.[28]	Cortical involvement, ASPECTS score	Cortical involvement, ASPECTS score	–
Hundozi et al.[29]	Low/normal blood pressure, younger age	Not reported	Higher ES rate in recurrent strokes
Conrad et al.[30]	High NIHSS	Not reported	–
Hamidou et al.[31]	HS, SAH, impaired consciousness, higher blood glucose on admission	Not reported	Not associated with mortality/worse clinical outcome
Couillard et al.[32]	Single-vessel anterior circulation involvement, atrial fibrillation, hemorrhage	Not reported	Mortality was associated with ES
Strzelczyk et al.[33]	PoSERS scale	Not reported	The PoSERS appears to be a valuable tool to predict the risk for PSE within the first few days after a stroke
de Reuck et al.[34]	No independent predictors	Not reported	–
Stefanodou et al.[35]	Moderate and severe disability	Not reported	–
Cheung et al.[36]	Male gender, cortical location (anterior)	Cortical location	–
Kammersgaard et al.[37]	Not reported	Younger age, intracerebral hemorrhage, lesion size, increasing stroke severity, ESs	–
Labovitz et al.[38]	HS, lobar lesion	Not reported	ES was not associated with worse clinical outcome
Lamy et al.[39]	Higher Rankin scale, cortical involvement	ESs, cortical signs, and large infarct	–
Cordonnier et al.[40]	No independent predictor	Stroke severity, pre-existing dementia	Stroke patients with pre-existing dementia have an increased risk of LSs
Bladin et al.[41]	HS, severe stroke, cortical location	HS, severe stroke, cortical location	Higher mortality in patients with seizures; LSs were associated with epilepsy/recurrent seizures
Serafini et al.[42]	Hyponatremia, hemorrhagic transformation	Younger age, cortical stroke	ES was not associated with worse clinical outcome
Dewan et al.[43]	Not reported	Not reported	ES was not associated with early mortality
Panitchote et al.[44]	HS, cortical location, non-dyslipidemia	Not reported	–
Goswami et al.[45]	Alcoholism, HS, cortical location, severe stroke	Not reported	Hypertension, alcoholism, ES, and hemorrhagic stroke predicted early disability or death
Aiwansoba et al.[46]	More frequent in IS	Not reported	–
Pezzini et al.[47]	Stroke severity on admission, cortical involvement, stroke subtype	Not reported	Lower burden of complications among stroke patients who did not develop ES

(*Continued*)

https://doi.org/10.1017/S1092852919000804 Published online by Cambridge University Press

TABLE 2. (*Continued*)

Study	Risk factors of ESs	Risk factors of LSs/epilepsy	Other findings
Procaccianti et al.[48]	Total anterior circulation infarct, hemorrhagic transformation, hyperglycemia	Not reported	ES may be considered a marker of stroke severity.
Mecarelli et al.[49]	Not reported	Not reported	EEG monitoring should be performed in order to detect purely electrographic seizures
Beghi et al.[50]	HS, cortical lesion	Not reported	Higher 30-day mortality rates in patients with ES
Misirli et al.[51]	Younger age, cortical lesion, cardioembolic stroke	Not reported	–
Dhanuka et al.[52]	Not reported	Late onset seizures were associated with recurrent seizures	Early onset seizures did not recur and affect clinical outcome
Leys et al.[53]	Older age, higher BP, cardioembolic stroke, rtPA type	Older age, higher NIHSS, higher blood pressure, hemorrhage	The neurotoxic effect of rtPA has very little influence on outcome in humans
De Reuck and Van Maele[54]	History of previous stroke, dependence rate	History of previous stroke, dependence rate	–

ASPECTS, Alberta Stroke Program Early CT Score; BP, blood pressure; ES, early seizure; HS, hemorrhagic stroke; IS, ischemic stroke; ICH, intracerebral hemorrhage; NIHSS, NIH Stroke Scale; SAH, subarachnoid hemorrhage.

Twelve studies covering 188 patients including four case reports and eight single-center studies reported CTP changes in seizures[14,59,81-90] (Table 6). Their results are relatively homonymous: focal hypo- or hyperperfusion or large hemispheral hypo –or hyperperfusion (usually sparing the basal ganglia) in atypical vessel pattern/non-corresponding vessel distribution could be detected. Comparing the CTP results of 17 stroke and 12 seizure patients, time to peak (TTP) parameter can be helpful in the differentiation of ischemia vs. seizure.[88]

There are limited reports in association with MRI perfusion and seizures. Three case reports detected DWI hyperintensity and hyperperfusion in the temporal lobe of patients with SE.[91-93] Aphasic SE is also associated with temporoparietal DWI hyperintensity with corresponding hyperperfusion.[68] Arterial spin labeling (ASL) MRI seems to be a promising technique in the identification of epileptic foci.[94,95]

Seizures and thrombolysis

In their retrospective study, Couillard et al. reported predictors of ESs, analyzing the clinical data of 400 thrombolyzed patients.[32] The detected low seizure rate which was comparable to previous studies suggested tPA in itself is not a risk factor. ES rate was also low in two studies confirming their findings.[24,28] De Reuck and Van Maele also could not find association between treatment modality and occurrence of seizures.[34] However, systemic thrombolysis was a significant predictor of ESs in two studies including a multicenter trial[11,53] (Table 1).

Treatment of early seizures

Twelve studies reported on antiepileptic treatment of ESs.[19,20,23,27,30,32,39,40,51,54] Therapy was started in 79.3% (276/348).[19,23,27,32,39,40,50,51] This rate was 37.9% (33/87) in IS patients.[19,27,32,39] Carbamazepine, valproic acid, and phenytoin were the most commonly prescribed drugs[20,26,27,32,39,40,54] (Table 3).

Discussion

Based on our review article analyzing the data of 37 studies including more than 36,000 patients, we can conclude that ES rate was pretty low (4.4% overall). As vast majority of these studies included patients with IS and other stroke subtypes, we calculated ES rate in IS if reported. This was 3.8%, which was comparable to the existing literature.[3,96] However, significant geographical differences could be found in the occurrence of ES, and there was a three-fold increase in Asian and African populations compared to European and Northern-American studies, which has been previously unreported. Despite extensive literature search, we could not find obvious explanation to these phenomena. Possibly, differences in stroke services and the more frequent occurrence of concomitant diseases (especially infections and metabolic changes) can elucidate these findings.[22,31,42,48]

Cortical involvement, large lesion, severe stroke, hemorrhagic transformation, younger age (<65 years), and atrial fibrillation were the most important risk factors of ES in IS. Metabolic disturbances such as low sodium or elevated plasma glucose can also precipitate seizures lowering the threshold. A recent meta-analysis (including

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TABLE 3. Early seizure type

Study population	Seizure type			Within 24 h	SE	Treatment
	Simple partial	Complex partial	Generalized			
Kim et al.[19]	25/48		23/48	37/48	13/48	7/48 was not treated, no report on treatment
Bryndziar et al.[20]	23/35 not reported in ES		12/35 not reported in ES	7/14	2/14	Phenytoin was the most commonly prescribed drug (70%)
Mohamed et al.[21]	Not reported	Not reported	Not reported	Not reported	8/47	Not reported
Wang et al.[22]	77/232 not reported in ES	75/232 not reported in ES	80/232 not reported in ES	Not reported	Not reported	Not reported
Arntz et al.[23]	25/76 not reported in ES	25/76 not reported in ES	25/76 not reported in ES	Not reported	Not reported	12/25 not treated, no report on treatment
Jung et al.[24]	10/26	0/26	16/26	Not reported	Not reported	Not reported
Khealani et al.[26]	Not reported	Not reported	Not reported	Not reported	Not reported	Phenytoin and valproic acid were most commonly prescribed AEDs followed by carbamazepine
Cordonnier et al.[27]	3/9		5/9	Not reported	1/9	4/9 were treated (2 with carbamazepine, 2 with valproic acid)
Conrad et al.[30]	9/23 not reported in IS		14/23 not reported in IS	Not reported	2/23 not reported in IS	Monotherapy started in more than 90% of patients
Couillard et al.[32]	5/16	4/16	4/16	Not reported	Not reported	14/16 with phenytoin
Stefanidou et al.[35]	18/25		7/25	9/12	Not reported	Not reported
Cheung et al.[36]	8/16 not reported in IS	1/16 not reported in IS	7/16 not reported in IS	Not reported	0/16	Not reported
Labovitz et al.[38]	4/37 not reported in IS	18/37 not reported in IS	9/37 not reported in IS	32/37 (13/37 at stroke onset)	10/37	Not reported
Lamy et al.[39]	9/14		5/14	10/14	2/14	8/14 received antiepileptic drugs immediately after ESs (5/14 valproic acid, 2/14 carbamazepine, and 1/14 phenytoin)
Cordonnier et al.[40]	6/11 not reported in IS		4/11	8/11 (6 at onset) no report in IS	1/11	4/11 received antiepileptic drugs (2/11 carbamazepine, 2/11 valproic acid)
Bladin et al.[41]	Not reported	Not reported	Not reported	66/168 not reported in IS	Not reported	Not reported
Aiwansoba et al.[46]	14/25 not reported in IS		11/25 not reported in IS	Not reported	2/25 not reported in IS	Not reported
Pezzini et al.[47]	13/20 not reported in IS		7/20 not reported in IS	Not reported	2/20	Not reported
Procaccianti et al.[48]	33/66 not reported in IS	6/66 not reported in IS	27/66 not reported in IS	39/66 not reported in IS	13/66 not reported in IS	Not reported
Mecarelli et al.[49]	Not reported	Not reported	Not reported	15/15 not reported in IS	10/15 not reported in IS	Not reported
Beghi et al.[50]	30/45 not reported in IS		15/45 not reported in IS	33/45 not reported in IS	Not reported	27/45 no report on treatment
Misirli et al.[51]	116/200 not reported in IS		84/200 not reported in IS	Not reported	Not reported	Monotherapy was used in 169/200 and polytherapy in 31/200 patients
Dhanuka et al.[52]	Not reported		Not reported	17/27	1/27	Not reported
Leys et al.[53]	15/18		3/18	Not reported	Not reported	Not reported
De Reuck and Van Maele[54]	118/195 not reported in ES	35/195 not reported in ES	42/195 not reported in ES	Not reported	26/195 not reported in ES	Carbamazepine was used in 1/3 of patients

AED, antiepileptic drug; ES, early seizure; IS, ischemic stroke.

https://doi.org/10.1017/S1092852919000804 Published online by Cambridge University Press

TABLE 4. EEG findings in ES

	EEG findings			
Study	Normal	Diffuse slowing	Focal slowing	PLED/epileptiform discharge
Kim et al.[19]	20/116	17/116	59/116	20/116
Bryndziar et al.[20]	2/19	7/19	7/19	Not reported
Wang et al.[22]	0/123	51/123	21/123	51/123
Khealani et al.[26]	14/89	38/89	23/89	14/89
Conrad et al.[30]	10/23	10/23		3/23
Beghi et al.[50]	0/34	22/34		12/34
Dhanuka et al.[52]	12/35	9/35	8/35	6/35
De Reuck and Van Maele[54]	11/24	9/24	2/24	2/24
Gupta et al.[55]	2/20	6/20	10/20	2/20
Horner et al.[56]	4/17	0/17	9/17	4/17
De Reuck et al.[57]	13/59	17/59	17/59	12/59
Velioglu et al.[58]	0/180	47/180		133/180

PLED, periodic lateralized epileptiform discharge.

TABLE 5. MRI diffusion-weighted imaging findings in seizure

Study	Study type	Patient number	Findings
Hufnagel et al.[61]	Single-center	9	ADC decreased in the epileptogenic zoneGeneralized ADC changes after generalized seizures
Konermann et al.[62]	Single-center	12	ADC decreased in the hippocampus on the seizure-onset side and in the parahippocampal gyrus on both sides
Senn et al.[63]	Case report	1	ADC was higher in the affected hemisphere than on the other side
Szabo et al.[64]	Single-center	10	Regional hyperintensity on DWI, and a reduction of the ADC in the hippocampal formation, the pulvinar region, and cortical regions
Hong et al.[65]	Case report	1	ADC showed an increased signal in the left temporoparietal area
Parmar et al.[66]	Single-center	10	DWI showed increased hippocampal signal and a decreased ADC in the same region
Miligan et al.[67]	Single-center	10	Increased signal on DWI in the hippocampus ipsilateral to the seizure focus Variably restricted diffusion in the splenium and in gyral distribution
Toledo et al.[68]	Single-center	8	Cortical temporoparietal hyperintensity in DWI and ipsilateral pulvinar lesions
Lee et al.[69]	Case report	1	Hyperintensity lesions on DWI in the splenium and in the right parietal lobe
Di Bonaventura et al.[70]	Single-center	10	DWI images revealed significant signal alterations depending on the location of ictal activity
Kumral et al.[71]	Single-center	76	Multiple DWI changes and recurrent and longer poststroke seizures were strongly associated
Maalouf and Keyrouz[72]	Case report	1	Left temporal diffusion restriction
Chatzikonstantinou et al.[73]	Single-center	56	DWI hyperintensity in the hippocampal and pulvinar region ipsilateral to the epileptogenic brain lesion Bilateral DWI lesions
Koo et al.[74]	Case report	1	DWI hyperintensity in the right thalamus
Cartagena et al.[75]	Single-center	10	Diffusion changes in the hippocampal region, thalamus, basal ganglia, brain stem, and cerebellum
Ohe et al.[76]	Single-center	10	Bi- or unilateral DWI hyperintensity, cortical DWI hyperintensity
Cianfoni et al.[77]	Single-center	26	Diffusion abnormalities in the hippocampus, cortical/subcortical region, basal ganglia, white matter, corpus callosum, cerebellum
Rennebaum et al.[78]	Single-center	69	Cortical and thalamic DWI restriction
Williams et al.[79]	Case series	4	Diffusion restriction and reduced ADC in one or both hippocampi and the splenium of the corpus callosum
Jabeen et al.[80]	Single-center	30	Hippocampal, perisylvian, thalamic, splenium, and cortical DWI changes

ADC, apparent diffusion coefficient; DWI, diffusion-weighted imaging.

https://doi.org/10.1017/S1092852919000804 Published online by Cambridge University Press

TABLE 6. CT perfusion findings in seizure

Study	Study type	Patient number	Findings
Wiest et al.[81]	Single-center	15	Temporal, parietal, or frontal hyper- or hypoperfusion
Hedna et al.[14]	Case report	1	Reduced time to peak (TTP), increased CBF, and CBV
Gelfand et al.[82]	Single-center	27	Focal hypoperfusion, with prolonged MTT and decreased CBF and CBV with no corresponding arterial territory/atypical vessel pattern
Hauf et al.[83]	Single-center	19	Increased regional CBF, increased regional CBV, and decreased MTT
Masterson et al.[84]	Case series	4	Perfusion CT revealed increases in CBF and CBV as well as a decreased MTT, consistent with hyperperfusion
Mathews et al.[85]	Case report	1	Reduction in CBF and blood volume involving the entire left hemisphere
Royter et al.[86]	Case report	1	Hyperperfusion in the right frontoparietal region
Austein et al.[59]	Single-center	37	Cortical hyperperfusion or hypoperfusion pattern with a cortical–subcortical involvement typically crossed the normal anatomical vascular territories boundaries
Shelly et al.[87]	Single-center	25	Specific reduction in CBV and CBF
Kubiak-Balcerewicz et al.[88]	Single-center	29	TTP was significantly different in stroke and seizure patients
López Ruiz et al.[89]	Single-center	11	Increased TTP in multilobar cortical locations in the absence of large-vessel occlusion and basal ganglia involvement
Payabvash et al.[90]	Single-center	18	Focal, unilateral hyperperfusion – increased relative CBF (rCBF) and volume (rCBV), which most often affected the temporal lobe

all types of strokes) concluded that hemorrhagic stroke (significantly higher occurrence compared to IS) and cortical involvement are the most important risk factors of poststroke seizures.[97] It is a matter of debate whether an ES is a marker of stroke severity or not.[24]

ES tends to be focal (more likely simplex partial than complex partial) at onset in about two-thirds of all patients and general in the remaining one-third. Sixty percent occur within 24 h and it is possible that 40% of all seizures are presented at the onset of stroke symptoms raising the possibility of other etiology, requiring an extensive diagnostic workup.[38,40,98] Aphasic SE or postictal confusion with paresis is indistinguishable from IS in patients with dementia or aphasia.[68]

EEG is not routinely available in the emergency rooms and the procedure takes time causing significant delay in acute stroke treatment. Furthermore, EEG is not really helpful apart from the detection of seizure patterns or non-convulsive SE as based on our results, about one-fifth of all ES patients had negative EEG findings and seizure-like activity could be detected only in approximately 18%. On the other hand, abnormal EEG findings can be detected in vast majority of acute stroke patients and seizures are presented in about one-third in patients with PLED/epileptiform discharge.[49,99,100]

Plain brain CT has no place in the detection of seizures vs. ischemia. In patients with severe neurological symptoms, CTA can be helpful to pick up large-vessel occlusion but unable to detect hyperacute small vessel pathology or lacunar strokes.[60,101] Nevertheless, it only takes 10 additional minutes to perform to diagnose an intracranial occlusion and also gives information of the vascular status and extent of parenchymal ischemic injury, extracted from CTA source imaging.[60,102,103]

MRI DWI is the most sensitive and specific imaging technique for the visualization of an acute infarct, with excellent sensitivity and specificity within minutes after the onset of symptoms.[103] MRI DWI seems to be helpful to distinguish between stroke and stroke mimics, which can be responsible for one quarter of all stroke ward admissions.[103–105] However, diffusion restriction can be detected in the hippocampal, thalamic, and callosal region in a considerable amount of seizure patients and in various cortical regions based on our literature search, but usually these lesions are not restricted to vascular territories.[106,107] Finally, MRI DWI can be negative in a small (~7%), but significant percentage of stroke patients, especially in strokes involving the posterior circulation.[108]

CT and MR perfusions are promising imaging techniques in the detection of regional differences in blood flow, thereby able to differentiate the ischemic penumbra from the infarct core, which can be useful in patients with SUTO or patients with extended time window who are usually opted out from treatment.[12] They are potentially useful imaging techniques helping to determine candidates for systemic thrombolysis or revascularization.[12,109]

CTP involves a continuous imaging over a minute during the administration of a relatively large amount of bolus of contrast by monitoring the first pass of the contrast through the cerebral vasculature.[110] Its advantage includes wide availability and short detection time, while it is associated with relatively large radiation dose and potential contrast-related side effects. It visualizes different derived color maps such as cerebral blood volume (CBV – the total volume of blood flowing through a voxel of interest in a given unit of time), cerebral blood flow

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(CBF – the total blood volume within the voxel of interest), mean transit time (MTT – mean time taken for a contrast to pass through the voxel of interest and is equivalent to CBV/CBF), and TTP(time taken to reach maximal contrast enhancement). In IS, the core has a decrease in both CBF and CBV, whereas the penumbra demonstrates a reduction in CBF with a relatively maintained CBV with corresponding vessel distribution. Tissue at risk of infarction will also have elevated MTT.[110,111] In contrast, seizures are associated with focal or large hemispheral hypo- or hyperperfusion on CBV/CBF sequences (usually sparing the basal ganglia) in non-corresponding vessel distribution without MTT or TTP changes, which can be helpful in the differentiation of ischemia vs. seizure.[87,88]

MR perfusion includes T1 signal intensity from baseline also through the period of contrast inflow to estimate the same parameters.[111] If intravenous contrast is contraindicated, an MR technique called ASL may obtain perfusion mapping for acute stroke.[111] The same changes can be detected as in the case of CTP, and it can also identify the tissue at risk which can be salvageable. There is very limited evidence which suggests that seizures can be accompanied by temporal hyperperfusion detected by MR perfusion technique.

Rodan et al. raised the possibility of thrombolysis-induced seizures in their case report.[112] We found six studies with controversial results. A recent meta-analysis (including four out of the mentioned six studies) found no association between the application of rt-PA and the occurrence of seizures.[113] However, the recent multicenter OPHELIE trial suggested its association with ES.[53] Rt-PA has many properties beyond its thrombolytic activity, including control of neuronal survival, homeostasis of the blood–brain barrier, inflammation, axonal damage, and demyelination.[113] A specific cleavage at the Arg275-Ile276 peptide bound converts the single-chain (sc) form of tPA into a two-chain (tc) form, which have similar thrombolytic properties, but the sc form promotes NMDA receptor signaling (with increased neurotoxicity, potentially lowering seizure threshold), while the tc form downregulates this signaling pathway.[53,114] The above-mentioned OPHELIE trial raised the possibility that the ratio of sc/(sc 1 tc) rtPA >80.5% can be associated with ES.[53] This trial was not included in the recent meta-analysis.[113]

The impact of ES on clinical outcome is also controversial: eight studies reported ESs as predictors of worse clinical outcome, while seven studies showed neutral effect. However, the meta-analysis of Xu et al. suggested higher risks of both mortality and disability in a large cohort of poststroke patients.[115] It is possible that ESs are the markers of stroke severity and by this are associated with worse clinical outcome.[24] On the other hand, a significant proportion of patients can develop SE, which can be as high as 16% based on our results. It is well known that SE is associated with higher fatality rates and unfavorable clinical outcome.[116]

The AHA and ESO guidelines stated against the routine use of antiepileptic drugs in ES and there is also insufficient evidence with regard to the initiation and type of antiepileptics (if required).[117,118] There is no evidence of immediate primary prophylaxis in ES, but based on our results about 40% of these patients were treated. Carbamazepine, valproic acid, and phenytoin were the most commonly prescribed drugs. The only trial (although focusing on LSs) found similar efficacy between carbamazepine and levetiracetam, the latter has advantages on cognitive functions.[118] However, a significant proportion of patients can develop SE and ES may be a risk factor of PSE.[16]

Strzelczyk et al. assessed their PSE risk scale (PoSERS) within a follow-up of 1 year.[33] Data on 10 risk items concerning the stroke localization, stroke subtype, stroke severity, hemorrhagic transformation, previous vascular encephalopathy, early- and late-onset seizures were collected using a PSE risk scale (PoSERS), which showed moderate sensitivity and positive predictive value while specificity and negative predictive value were relatively high, if only ESs within 24 or 48 h were considered, maybe promoting clinicians' decision with regard to treatment initiation.[33]

In conclusion, we overtook a systematic and in-depth review on ESs after IS. ESs are rare complications of acute stroke with substantial burden. A significant proportion can be presented at the onset of stroke requiring an extensive diagnostic workup. Multimodal brain imaging can be helpful in the differentiation of seizure vs. ischemia. Large, multicenter trials are needed to evaluate the role of different variables on seizure risk and to evaluate the initiation and type of optimal treatment.

Availability of data and materials

The dataset supporting the conclusions of this article is available on request to the corresponding author.

Disclosures

The authors declare that they have nothing to disclose.

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https://doi.org/10.1017/S1092852919000804 Published online by Cambridge University Press

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