Poststroke Epilepsy

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DEFINITION

- Acute symptomatic seizures
- Late poststroke seizure
- Poststroke epilepsy

Epilepsia, 51(4):671–675, 2010
doi: 10.1111/j.1528-1167.2009.02285.x

SPECIAL REPORT

Recommendation for a definition of acute symptomatic seizure

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SUMMARY

a diagnosis of acute symptomatic seizure should be

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"Acute symptomatic seizure is defined as a clinical seizure occurring at the time of a systemic insult or in close temporal association with a documented brain insult. Suggestions are made to define acute symptomatic seizures as those events occurring within 1 week of stroke, traumatic brain injury, anoxic encephalopathy, or intracranial surgery"

hematoma; at the presence of an active central nervous system (CNS) infection; or during an active phase of multiple sclerosis or other autoimmune diseases. In additi

bolic dysfunction still require a clear identification.

KEY WORDS: Epidemiology, Definition, Acute, symp-

Beghi E, et al. Epilepsia, 51(4):671–675, 2010

- Acute symptomatic seizures

: seizures occur within one week after acute stroke

- Late poststroke seizure

: unprovoked seizure that occurs > 1 week after acute stroke

- Poststroke epilepsy

ILAE OFFICIAL REPORT

A practical clinical definition of epilepsy

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Epilepsia, 55(4):475–482, 2014
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SUMMARY

Epilepsy was defined conceptually in 2005 as a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures. This definition is usually practically applied as having two unprovoked seizures >24 h apart. The International League Against Epilepsy (ILAE) accepted recommendations of a task force altering the practical definition for special circumstances that do not meet the two unprovoked seizures criteria. The task force proposed that epilepsy be considered to be a disease of the brain defined by any of the following conditions: (1) At least two unprovoked (or reflex) seizures occurring >24 h apart; (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; (3) diagnosis of an epilepsy syndrome. Epilepsy is considered to be resolved for individuals who either had an age-dependent epilepsy syndrome but are now past the applicable age or who have remained seizure-free for the last 10 years and off antiseizure medicines for at least the last 5 years. "Resolved" is not necessarily identical to the conventional view of "remission or "cure." Different practical definitions may be formed and used for various specific purposes. This revised definition of epilepsy brings the term in concordance with common use.

KEY WORDS: Epilepsy, Seizure, Definition, Unprovoked, Recurrence.

Table 2. Operational (practical) clinical definition of epilepsy

Epilepsy is a disease of the brain defined by any of the following conditions

1. At least two unprovoked (or reflex) seizures occurring >24 h apart
2. One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years
3. Diagnosis of an epilepsy syndrome

Epilepsy is considered to be *resolved* for individuals who had an age-dependent epilepsy syndrome but are now past the applicable age or those who have remained seizure-free for the last 10 years, with no seizure medicines for the last 5 years.

Its intent is to encompass circumstances for which some practitioners and expert epileptologists manage patients as if epilepsy is present after a single unprovoked seizure, because of a very high risk of recurrence.
Such examples may include patients with a single seizure occurring at least a month after a stroke or a child with a single seizure conjoined with a structural or remote symptomatic etiology and an epileptiform electroencephalography(EEG) study

Epilepsia, 50(5):1102–1108, 2009
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FULL-LENGTH ORIGINAL RESEARCH

Is a first acute symptomatic seizure epilepsy? Mortality and risk for recurrent seizure

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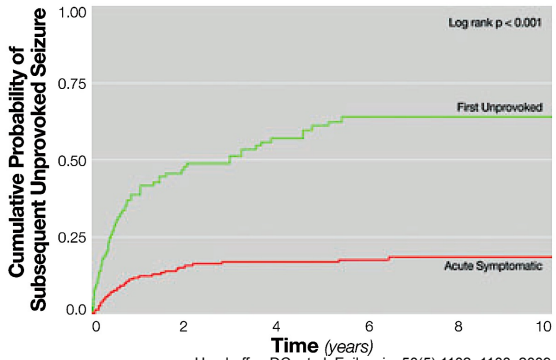
Hesdorffer, DC, et al. Epilepsia, 50(5):1102–1108, 2009

- To compare mortality and subsequent unprovoked seizure risk in a population-based study of acute symptomatic seizure and first unprovoked seizure due to static brain lesions
- Subjects were residents of Rochester, Minnesota, identified through the Rochester Epidemiology Project's records-linkage system between 1/1/55 and 12/31/84.
- Information was collected on age, gender, seizure type, etiology, status epilepticus (SE), 30-day and 10-year mortality, and subsequent episodes of unprovoked seizure.

Hesdorffer, DC, et al. Epilepsia, 50(5):1102–1108, 2009

- 262 individuals experienced a first acute symptomatic seizure and 148 individuals experienced a first unprovoked seizure, all due to static brain lesions.



Hesdorffer, DC, et al. Epilepsia, 50(5):1102–1108, 2009

Risk of subsequent unprovoked seizure

	Acute symptomatic seizure	First unprovoked seizure	p
Stroke	33.0% (95% CI = 20.7–49.9%)	71.5% (95% CI = 59.7–81.9%)	p = 0.001
Traumatic brain injury	13.4% (95% CI = 7.0–24.8%)	46.6% (95% CI = 30.4–66.3%)	p < 0.001
CNS infection	16.6% (95% CI = 9.5–28.0%)	63.5% (95% CI = 21.2–98.6%)	p = 0.010

Hesdorffer, DC, et al. Epilepsia, 50(5):1102–1108, 2009

- Acute symptomatic seizures
- Late poststroke seizure
  =?
- Poststroke epilepsy

" The new definition is not uncontroversial, mostly due to conflicting data on the actual recurrence risk of seizures after a first late-poststroke seizure and whether a diagnosis benefits patients"

EPIDEMIOLOGY OF POSTSTROKE EPILEPSY

- long-term cumulative risk of PSE after a cerebrovascular event varies between 2% and 13%

- Both early and late seizures are more common after hemorrhage than after infarctions, with the exception of total anterior circulation infarctions

Study	n	Study type	Percentage IS/ICH/SAH	Follow up (mean or total)	Outcome measure	Cumulative risk
So *et al.* [1996]	535	Retrospective	100/0/0	5.5 yrs	PSE: 2 sz	IS: 8.9% 10-yr risk
Burn *et al.* [1997]	675	Retrospective	81/10/5	>2 yrs	All seizures > 24 h	All: 11.5%, IS 9.7%, ICH 26.1%, SAH 34.3% [5-yr actuarial risk]
Paolucci *et al.* [1997]	306	Prospective [rehab inpatient]	81/19/0	No data	1 LS	All: 15% IS: 12% ICH: 27%
Bladin *et al.* [2000]	1897	Prospective	86/14/0	9 mths	PSE: 2 sz	All: 2.5%, IS: 2.1%, ICH: 2.6%
Lossius [2002]	482	Prospective [age > 60]	92/8/0	12 mths	PSE: 2 sz after 4 weeks	All: 2.5% PSE
Lamy *et al.* [2003]	581	Prospective [age 18–55]	100/0/0	37.8 mths	PSE: 2 sz	IS: 2.3% 3-yr risk
Kammersgaard and Olsen [2005]	1195	Prospective	93.7/6.3/0	7 yrs	PSE: 2 sz and need of AED	All: 3.2%
Okuda *et al.* [2012]	448	Retrospective [rehab inpatient]	64/36/0	8 mths	PSE: 2 sz	All: 1.3%
Arntz *et al.* [2013b]	697	Prospective [age 18–50]	93 incl TIA/7/0	9.1yrs	PSE: 2 sz	All: 7%, IS: 8%, TIA: 4%, ICH 23%
Graham *et al.* [2013]	3310	Prospective	73.4/13.8/5.7	3.8 yrs	PSE: 2 sz	All: 12.4%, IS: 4.4–28.7%, ICH: 18.2%, SAH: 21.7% estimated 10-yr risk
Jungehulsing *et al.* [2013]	1020	Prospective	87/8.7/3.8*	2 yrs	LS > 1 week	All: 8.2% 2-yr risk
Qian *et al.* [2014]	935	Prospective	0/100/0	1–16 yrs	PSE: dx in records	7%
Guo *et al.* [2015]	1832	Prospective	100/0/0	2.5 yrs	PSE: 2 sz	IS: 5%
Bryndziar *et al.* [2015]	489	Retrospective	100/0/0	6.5 yrs	LS > 2 week	IS: 4.4% LS
Serafini *et al.* [2015]	782	Prospective	79.28/14.83/3.2	2 yrs	PSE: 2 sz	All: 2.22%, IS 1.97%, ICH: 4.35%
Hultunen *et al.* [2015]	876	Retrospective	0/0/100	76 mths	PSE: 1 LS > 1 week	SAH: 12% 5-year risk of LS and AED

*Aetiology data only provided for 725 survivors.
IS, ischaemic stroke; ICH, intracerebral haemorrhage; SAH, subarachnoid haemorrhage; PSE, poststroke epilepsy; AED, antiepileptic drug; LS, late seizures; sz, seizures; dx, diagnosis.

	Cumulative risk at the end of the study (3-10 yrs)	Remarks
Overall risk	3.2 (7 yrs) 12.4% (10 yrs)	Include series with follow up>3 yrs
Ischemic stroke	2.3% (3 yrs) 4.4% (10 yrs) 8% (9 yrs)	Include prospective series with follow up > 3 yrs
ICH	18.2%(10 yrs) 23% (9 yrs)	Include only series with adequate no. of ICH with follow up > 3 yrs
SAH	12.5% (5 yrs) 21.7% (10 yrs)	Include only series with adequate no. of SAH with follow up > 3 yrs

Study	Predictors in all patients (mixed aetiology)	Predictors in IS	Predictors in ICH	Comment
Paolucci *et al.* [1997]	Putaminal haemorrhage Lobar haemorrhage Severity of stroke Young age [<46 yrs]			Rehab inpatients
Graham *et al.* [2013]	Young age [<65 yrs] Stroke subtype Cortical signs Stroke severity			
Bladin *et al.* [2000]	Late seizures [>2 weeks)	Late seizures		
Kammersgaard and Olsen [2005]	Young age Onset stroke severity Lesion size Haemorrhagic stroke Early seizure			
Serafini *et al.* [2015]	Young age Cortical location			
Lossius [2002]	Stroke severity			
Lamy *et al.* [2003]		Early seizure Cortical sign Lesion size		In young adults with cryptogenic stroke
Qian [2014]			Subcortical location Age (inversely) Hematoma evacuation	Predictors of late seizures

IS, ischaemic stroke; ICH, intracerebral haemorrhage.

Zelano J. Ther Adv Neurol Disord 2016; 9:424–35

- Predictors include
  - Stroke severity
  - Cortical symptoms
  - Hemorrhage
  - Total anterior circulation infarcts
  - Young age at stroke
  - Early seizures

Causes of SE from different series

	Patients, %						
Variable	Richmond, Virginia[1b]	Rochester, Minnesota[4]	French-Speaking Switzerland[5]	Hessen, Germany[6]	California[7]	Bologna, Italy[8]	London, United Kingdom[1c]
Low AED levels	21 (P)/34 (A)	1	8.1[d]	8.7	3.9	NA	0.5
CNS infections	52 (P)/5 (A)	8.5	NA	0	0.6	NA	10.2
Febrile	NA	8	14.9[e]	0	2.5	NA	32
Cerebrovascular disease	10 (P)/22 (A)	19.1	30.5[f]	66.7	12.4	41	0.5
Alcohol abuse	13 (A)	NA	NA	8.7	8.1	7	0
Trauma	3 (A)	4.5	NA	7.3	0.4	10	1.5
CNS tumors	7 (A)	NA	NA	12	1.8	5	NA
Metabolic disturbance	5 (P)/15 (A)	3.5	NA	8.7	8.7	24[g]	3
Degenerative brain disease/ CNS anomalies	38 (P)/25 (A)	5.5	NA	26.7	13.3	10	32
Medication induced/overdose	2 (P)/3 (A)	2	NA	10.7	NA	NA	1
Anoxia/hypoxia	5 (A) (anoxia) 5(P)/ 13 (A) (hypoxia)	10	Excluded	NA	8	9.1	0.5
Cryptogenic	5 (P)/3 (A)	17.5	8.7	8.7	NA	11	11.7

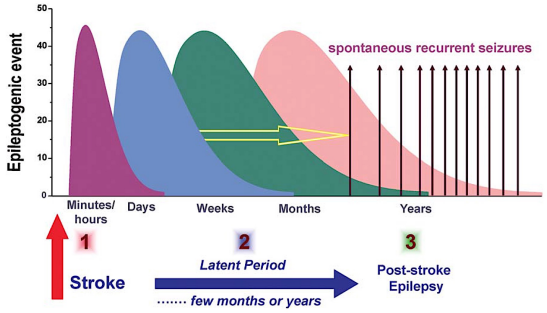
Neligan A. Arch Neurol 2010;67:931-40

Frequency and Mortality of SE

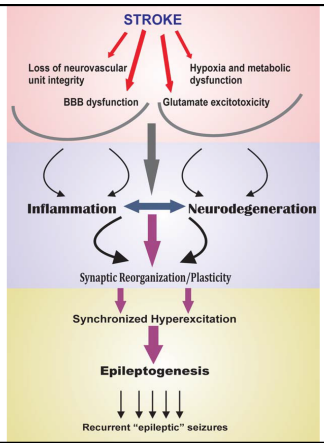
	Proportion of Cases of SE, %	Associated Acute Mortality in Patients With SE, %
Drug reduction/withdrawal, poor compliance, or low AED levels	10-20	0-10
Cerebrovascular disease	10-40	20-60
Metabolic disorders	5-15	10-35
Acute CNS infections[b]	0-10	0-30
Anoxia	5-10	60-100
Alcohol abuse	5-15	0-10
Head trauma	0-10	0-25
Drug overdose/toxicity	0-10	10-25
Brain tumors	0-10	0-20
Cryptogenic/idiopathic	5-15	5-20

Neligan A. Arch Neurol 2010;67:931-40

POSTSTROKE EPILEPTOGENESIS



Reddy DS, et al. J or Neurosci Res 2017;95:1000-16



TREATMENT

- There is no evidence to date that treatment with AEDs prevents the development of PSE and the risk of seizure after stroke is relatively low, so primary prevention is usually not appropriate
- Short-term treatment is often initiated if multiple early seizures occur or after a single seizure in cases of ICH or hemorrhagic transformation

- In the case of a late seizure, the patient should be informed of a high recurrence risk and offered seizure prophylaxis.
- Individual factors such as constant supervision, lack of ambulation and low risk of seizure-related injury, or very mild seizures, etc. may be reasons to defer treatment

AEDS SELECTION

- Antiepileptic drug selection should made in the same manner as for other forms of epilepsy.
- Potential drug interactions especially between enzyme inducing AEDs and drugs used in secondary prophylaxis should be considered.

Drug interaction with warfarin

- Metabolites through CYP3A4, 2C9
- Phenytoin, phenobarbital and carbamazepine reduce the concentration of warfarin by up to 50-65%
- Phenobarbital and carbamazepine also reduce the anticoagulation effects of warfarin metabolites
- Newer AEDs do not have signinificant interaction with anticoagulant

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Short communication

Interactions between non-vitamin K oral anticoagulants and antiepileptic drugs

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ABSTRACT

Atrial fibrillation (AF) is a frequent cause of stroke. Secondary prophylaxis by oral anticoagulants (OAC) is recommended after stroke in AF-patients. OAC can be achieved by vitamin-K antagonists (VKAs) or non-vitamin K antagonist oral anticoagulants (NOACs) like dabigatran, rivaroxaban, apixaban or edoxaban. Seizures are frequent after stroke, and antiepileptic drugs (AEDs) are indicated. The review, based on a literature research, aims to give an overview about pharmacokinetic knowledge and clinical data about drug–drug interactions (DDIs) between NOACs and AED.

Carbamazepine, levetiracetam, phenobarbital, phenytoin and valproic acid might decrease the effect of NOACs by inducing P-glycoprotein (P-gp) activity. Carbamazepine, oxcarbazepine, phenytoin, phenobarbital and topiramate might decrease the effect of NOACs by inducing CYP3A4 activity. Controversial data – inhibition as well as induction of CYP3A4 – were found about valproic acid.

The relevance of these DDIs is largely unknown since there are only sporadic case reports available. To increase the knowledge about DDIs between NOACs and AEDs we suggest subgroup analyses addressing effects and safety of VKAs versus NOACs in patients with AF on AEDs, in case they have been included in previously completed or still ongoing trials or registries. This could be easily feasible and would be desirable in view of the large data already accumulated.

Stollberger C, et al. Epi Res 2016;126:98-101

- Intestinal absorption and renal elimination of NOACs are dependent on the intestinal and renal permeability glycoprotein (P-gp) efflux transporter protein system
- Some NOACs are substrates of the hepatic CYP3A4 enzymes
- Induction of P-gp or CYP3A4 mightdecrease serum NOAC levels, reduce anticoagulant effects and lead to an increase in embolic risk.

NOAC	P-GP substrate	CYP 3A4 substrate
Dabigatran	Yes	No
Rivaroxaban	Yes	Yes
Apixaban	Yes	Yes
Edoxaban	Yes	Yes

Pharmacokinetic drug interactions mediated by P-gp alone (dabigatran) or in combination with CYP3A4 enzymes (rivaroxaban and apixaban) have been reported

Chin PK, Wright DF, Zhang M, et al. C. Drugs R. D. 2014;14: 113–23.
Hellwig T, Gulseth M. Ann. Pharmacother 2013;47: 1478–87.
Serra W, Li Calz M, Coruzzi P. Clin. Pract 2015; 5: 788

PROGNOSIS

- PSE is often described as an easily manageable form of epilepsy, where monotherapy suffices to control seizures
- However, only reports from small case series exist with varying results

Silverman et al. 2002, Bryndziar et al. 2015, Zelano et al. 2015

- Compared with the information on the risk of developing PSE, there is less information on morbidity or mortality associated with the condition.
- In patients aged 18–50, poststroke epilepsy was associated with increased mortality also after adjustment for confounders

Arntz et al. 2015

CONCLUSION

- Major cause of epilepsy after middle age
- Over the last decade, there have been remarkable improvements in the management of stroke, revascularisation, secondary prophylaxis, and rehabilitation.

- Post stroke epilepsy (PSE) thereby occurs in an optimistic medical context, but advances in management of poststroke seizures have not quite matched those seen in other stroke treatment domain.