

Seizures, epilepsy and vascular disorders

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ABSTRACT – Stroke is a major cause of seizures in the elderly. About 10% of all stroke patients experience one or several seizures; they may occur during the first 24 hours after the stroke, in the early and late stages and after several months or even years following the initial vascular accident. We review current data on epidemiology, risk factors, semiology, differential diagnosis, follow-up and recurrence, and management of seizures following stroke.

Keywords: stroke, epilepsy, seizures

Epileptic seizures occurring as a result of stroke are a significant complication of ischemic or hemorrhagic cerebrovascular accidents. They have been known for a very long time, as witnessed by the fact that as early as 1864 Jackson wrote: “It is not uncommon to find when a patient has recovered from hemiplegia, the result of embolism of the middle cerebral artery... that he is attacked by convulsions...”. Stroke is the main cause of epileptic seizures in subjects over the age of 60. Factors predisposing to the occurrence of seizures or of vascular epilepsy have been studied with renewed interest in the past few years, since the improvement of brain imaging techniques. Consensus has been reached regarding some of these factors, such as the hemorrhagic character of the stroke and the presence of a cortical lesion.

Depending on the interval between the onset of seizures and the occurrence of the stroke, seizures are classified as early or late. This interval also seems to influence the risk of developing vascular epilepsy.

Studies differ on their assessment of what are called vascular seizures. There are several reasons for this disparity: different length of follow-up period, the definition itself: seizure

and/or epilepsy, interval between initial seizure and stroke; heterogeneity of type of stroke (ischemic or hemorrhagic: some studies examine both simultaneously); different patient selection criteria (hospital, rehabilitation center, external patients), and the retrospective or prospective character of the study.

Epidemiology

The epidemiology of epileptic seizures is assessed very diversely, its frequency being estimated to be between 4% and 43%! This is due to several factors, some of which are listed below:

- The terms “seizure” and “epilepsy” are sometimes used interchangeably,
- Study objectives are very diverse, making meaningful comparisons impossible,
- Most studies are retrospective,
- Some studies did not include brain imaging such as MRI,
- For these reasons, stroke etiologies are uncertain and very heterogeneous. This is why we consider that only studies having made a complete survey, with good brain imaging showing the cerebral lesion clearly, to confirm etiology, should be taken into account;

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the nature of the mechanism should be explicit: ischemia or hemorrhage. Some etiologies should be excluded, namely those whose etiopathogenic seizure mechanisms are different: cerebral venous thrombosis, subarachnoid hemorrhage, subdural hemorrhage, extradural hematoma, vascular malformation, cerebral contusion, and epilepsy prior to stroke. If these criteria are respected, the following epidemiologic data appear to be clearly demonstrated:

1. Stroke is the major cause of epilepsy in the elderly (Granger *et al.* 2002, Hauser and Kurland 1975);
2. The interval between the occurrence of stroke and seizure is important: it influences, among other, the occurrence of subsequent seizure(s); but, to date, there is no consensus on the length of this interval. Many authors consider early seizures as being those that occur within 14 days after the stroke, and late seizures those that occur after 14 days; some authors distinguish contemporary seizures, that is, those that occur in the 24 hours following the stroke. Seizure etiopathogenesis differs depending on whether seizures occur within one interval or another. Most seizures occur before the 14th day after the stroke, with the great majority occurring in the first 24 hours following the stroke. Bladin *et al.* 2000 have shown clearly that 40% of seizures occur in the 24 hours following an ischemic stroke, that early seizures (before the 14th day) occur in 48% of stroke patients, and that 3.8% of patients present late seizures;
3. The great majority of seizures are partial (see *infra*);
4. Hemorrhage causes seizures much more often than ischemia does (see *infra*).

Etiology and predisposing factors

Several studies have demonstrated that hemorrhage is responsible for the occurrence of seizure(s) much more often than ischemia (Bladin *et al.* 2000, Sazgar and Shuaib 2002). Bladin *et al.* (2000) estimate that the risk of seizure after hemorrhagic stroke is twice as high; 10.6% of patients with hemorrhagic strokes developed a seizure, as opposed to 8.6% of patients with ischemic strokes ($p < 0.002$). However, the "epileptogenic" potential of cardio-embolic strokes is to be reconsidered (Kilpatrick *et al.* 1990, Davalos *et al.* 1992).

Lesion location also plays a role in the occurrence of a seizure. Cortical localization is associated with the highest risk (Hauser and Kurland 1975, Bladin *et al.* 2000, Kilpatrick *et al.* 1990, Davalos *et al.* 1992, Lamy *et al.* 2003), particularly large lesions (Lancman *et al.* 1993).

The third factor influencing seizure occurrence is handicap. Frequency of seizures after ischemic stroke is directly proportional to the severity of the handicap, based on the Rankin scale (Bladin *et al.* 2000, Kilpatrick *et al.* 1990, Lancman *et al.* 1993, Lamy *et al.* 2003, Berges *et al.* 2000). By contrast, in cases of hemorrhagic stroke, patients with seizure(s) have a lower Rankin score (Bladin *et al.* 2000).

Seizure semiology

Regardless of the time of seizure occurrence in relation to the time of the stroke, seizures are most often partial (36%) or partial with secondary generalization (28%); half of them being motor. Generalized seizures, or those considered generalized, are often classified in the absence of reliable information (Berges *et al.* 2000). Status epilepticus constitutes a separate category; occurring in about 1% of stroke patients. It especially occurs in the setting of severe handicap; sometimes being the initial epileptic event. The occurrence of status epilepticus in stroke patients is associated with a high mortality rate (up to 50%) (Rumbach *et al.* 2000, Velioglu *et al.* 2001).

Differential diagnosis

Differential diagnosis is made, of course, with diseases and conditions that could cause epileptic or non epileptic episodes in stroke patients. These may include therapeutic changes (*i.e.* Benzodiazepine withdrawal) and metabolic problems (*i.e.* abnormal carbohydrate metabolism). In the setting of post stroke seizures, two major situations must be kept in mind: first, the possible occurrence of paroxysmal abnormal movements following a stroke and simulating seizures (Benamer *et al.* 2000, Ghika *et al.* 1994, Kim 2001); second, "inhibitive" or "negative" seizures presenting with aphasia, motor, sensory or cognitive deficit (Thomas 1999).

Follow-up: seizures recurrence

There is a major controversy regarding the risk of seizures recurrence after a stroke; a possibility that has major therapeutic implications. Several reasons contribute to this dilemma. These may include the small number of prospective studies; the variable range of follow-up periods reported (six to 47 months); the lack of consensus regarding the crucial period for advent of recurrence (contemporary, two weeks, one month?, etc.). Seizures may recur several times in patients already treated or not.

In our series (Berges *et al.* 2000), we have identified 159 patients with epileptic seizures in a population of 3 205 stroke patients taken from a stroke registry (Moulin *et al.* 2000). Out of 135 patients who were followed for an average period of 47 months, 50.3% presented a new seizure (*table 1*). Recurrence was associated with late occurrence (beyond the 14th day after the stroke) of the initial seizure (Berges *et al.* 2000). Two other studies have examined recurrence. First, Lamy *et al.* 2003 studied a population of 581 patients aged 18 to 55 years, and presenting with ischemic strokes. They have shown that among the 20 patients who had seizures after the 7th day, 11 patients had seizures recurrence during the follow up

Table 1. Seizure recurrence after initial seizure.

	No recurrence	Recurrence	Single recurrence	Multiple recurrence
Early seizure n = 41	27 (66%)	14 (34%)	7	7
Late seizure n = 94	40 (42.5%)	54 (57.5%)	17	37

Early seizures: seizures occurring before the 14th day after stroke; late seizures: seizures occurring after the 14th day. The data apply to 135 patients with at least one epileptic seizure, who were followed for an average period of 47 months. These 135 patients were part of an initial population of 159 patients with at least one epileptic seizure following ischemic or hemorrhagic stroke; the 159 patients were taken from a vascular registry of 3205 patients (Berges *et al.* 2000).

period of 37.8 ± 7 months. The authors estimate that recurrence risk is 0.7% for one year, and 2.3% for 3 years. Second, Bladin *et al.* (2000) showed that out of 28 patients (10.6% of stroke patients) with hemorrhagic stroke, seven presented seizure after the second week, and that all seven patients had seizure recurrence. Among patients with ischemic strokes, 55% of those who had a seizure beyond the 14th day had seizure recurrence. Epilepsy developed in 2.5% of the global stroke population, and occurrence of the first seizure after the 14th day was the major risk factor. As for occurrence of mortality, the data is inconclusive. Follow-up studies are rare and causes of death can be varied. Finally, one question is yet to be answered: can an epileptic seizure be a risk factor for occurrence of stroke?

Therapeutic management

Should antiepileptic therapy be instituted in patients with one or several seizures after a stroke? We have to admit that at present we have no definitive answer to this question. As far as we know, there is no published data based on prospective studies presenting the risks and benefits of antiepileptic treatment based on type of stroke. Despite this lack of data, clinical reality shows that although, in general terms, one out of two patients will have a second seizure, prognosis is good in this so-called vascular epilepsy (Semah *et al.* 1998).

Conclusion

When dealing with vascular epilepsy, three major considerations should be kept in mind. 1) Rigorous definition of patients with vascular epilepsy, being those with evident ischemic or hemorrhagic stroke (by etiological and radiological work up); 2) even in the setting of hemorrhagic stroke, factors influencing recurrence and prognosis are still poorly understood; 3) as far as we know, there is no established consensus concerning the therapeutic strategy, thus flexibility is advised in this setting. □

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