



Stroke- the most important cause of the newly diagnosed epilepsy in the elderly

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Abstract

About 35% of all newly diagnosed epileptic seizures in people older than 60 years are caused by stroke. The incidence of the early epileptic seizures is 2.4–5.4%, and for the late seizures 3–4.5%. Seizures after stroke are most often simple partial seizures with or without secondary generalization, and less often complex partial seizures. In early seizure these are acute biochemical cellular changes, and in late seizures gliosis. Although the risk for developing epilepsy was 17–35% after early seizures, the risk of developing epilepsy after late seizures increased to 65–90%. Combination of coronary heart disease, hypertension and cardiovascular disease occur in 65% of patients over 75 year old. Intrahospital mortality in patients with stroke with epileptic seizures was 37.9% compared to patients without seizures (14.4%). Early seizures cause higher mortality than late seizures which can be explained by synergistic effect of the damaged tissue due to the seizure and vascular ischaemia. European authors in 2007 indicate that lamotrigine, lamotrigine and gabapentin were first line drugs, followed by topiramate and valproate in elderly patients. Oxcarbazepine and carbamazepine were not highly recommended because of the associated hyponatremia, cardiac disorders and interaction potentials. The standard antiepileptic drug for focal epilepsy is still carbamazepine, and valproate is most commonly used for generalized epilepsy- even in older patients. Epidemiological studies on epilepsy treatment in the elderly show steady increase in the number of patients. Therefore, elderly patients require special attention. Monotherapy in low doses is often sufficient, enzyme inducing drug are used too frequently.

INTRODUCTION

Epilepsy and epileptic seizures are one of the most common and most serious neurological conditions worldwide. Epilepsy currently affects 1–1.5% of elderly population, and its prevalence and incidence rise as the number of old people increases worldwide.

Currently, epileptic seizures are the third most common neurological disorder in the elderly. Only cerebrovascular disorders and dementias are more prevalent (1). Ramsay *et al.* (2) investigated the distribution of different seizure types among the elderly and found that focal seizures (simple partial and complex partial with or without secondary generalization) occurred most frequently (73%). Tonic clonic status epilepticus was more frequent in older patients than in younger adults. Convulsive status epilepticus (SE) occurred in 17.6% of vascular

epilepsy cases among the elderly (3), whereas non-convulsive SE was found most frequently in adults near 60 years of age (4).

STROKE AND EPILEPSY

About 35% of all newly diagnosed epileptic seizures in people older than 60 years are caused by stroke. Their coexistence worsens medical and social prognosis and worsens invalidity.

Until now it has been well established that epileptic seizures can be provoked not only as a result of stroke, but also as a presenting symptom of stroke as well as the risk factor for the future subclinical cerebrovascular disease (5).

There are different studies in the literature identifying incidence of epilepsy after stroke and taking all of them into account the incidence would be 3–15%.

The most important clinical studies connected to this topic comes from population based registers. One of the first performed is Rotterdam study, pointing that patients with stroke have increased risk to develop epilepsy (6). Hauser *et al.* have demonstrated that cerebrovascular disease count for 11% of epilepsy causes (7). Forsgren *et al.* show that in patients older than 60, etiology of epilepsy is known in 77% of the patients, with stroke being the cause of epilepsy in 45% of the patients (8). So *et al.* has determined that the most probable period to develop epilepsy is one year after stroke. Comparing people with stroke with age and sex matched controls there is a 17 times higher risk to develop epilepsy in stroke group (9).

At our department for Neurology we have retrospectively analyzed 1449 patients with epilepsy who were admitted during the year 2003 and 2004. 21.5% of the patients were older than 65 years. The etiology of the seizures was: cerebrovascular disease in 54.1%, alcoholism in 13.5%, trauma in 8.5%, primary tumors in 4.98%, metastatic tumors in 4.6% and meningoencephalitis in 1.4% of the patients (10) (Figure 1).

Concerning risk factors for first seizure after stroke, one study created a multivariate analysis model for remote, symptomatic seizures that included cortical involvement, lesion size and prior lesions. The risk for acute seizures included cortical involvement, alcohol consumption and hemorrhagic stroke and prior lesion on a CT scan (11). In the present studies cortical involvement is an independent risk factor (12), in other studies, epileptic seizures are connected to the size of ischaemic lesion (13). Lisette *et al.* have shown that the risk to develop early epileptic seizures increase up to 8 times in patients with cardioembolic stroke in the temporal gyrus or posterior central gyrus, and 5 times in patients with supra-marginal gyrus or superior temporal gyrus (14). Epilepsy is less common in cerebellar stroke of the deep cerebral structures, although there are some described seizures in those locations as well. Seizures are described also in lacunar infarcts in 1–3% (15).

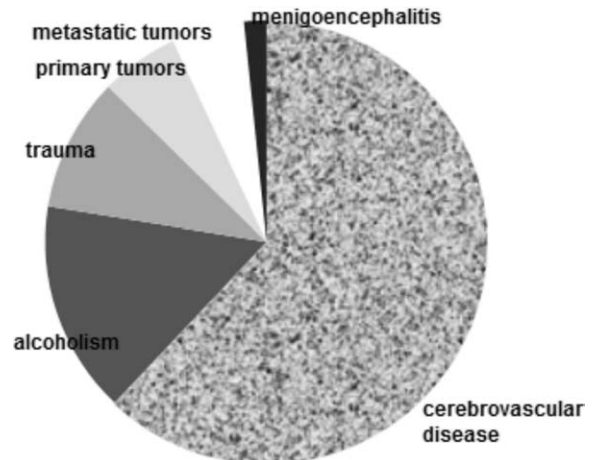


Figure 1. Etiology of epileptic seizures in 312 patients older than 65 years who were hospitalized during 2003–2004 at the University Department for Neurology, University Hospital Center „Sestre milosrdnice“, Zagreb, Croatia.

Epileptic seizures can trigger stroke meaning that epileptic seizures have to be taken seriously as a risk for developing stroke. The relative risk for developing stroke is 2.89 in patients with late onset seizure, the risk which could be compared to 1.4 risk with low HDL cholesterol (16).

Epileptic seizures can be the first symptom of stroke. Giroud *et al.* 1994 (17) has analyzed 90 patients with early epileptic seizures after stroke where 89% patients had seizures as the first symptom of stroke. In other studies early seizures after stroke have developed in 40–78% of the patients within 24 hours.

Seizures after stroke are most often simple partial seizures with or without secondary generalization, and less often complex partial seizures. In two out of nine studies it has been shown that generalized tonic clonic seizures develop more often after stroke. Haemorrhagic transformation in ischaemic stroke increases risk for developing seizures. Seizures that developed at the beginning of stroke were more often present in haemorrhagic infarct (19.2%) than cerebral haemorrhagia (15.6%) or ischaemic infarct (6.2%) (18).

EARLY AND LATE SEIZURES

Symptomatic epilepsy can be best described as ethiological reaction of the brain on the damage of all kinds. In patients with stroke there are two different types of epileptic seizures: early and late epileptic seizures.

As in posttraumatic epilepsy, there are different pathophysiological processes connected to early and late seizure onset after stroke. In early seizure these are acute biochemical cellular changes, and in late seizures gliosis.

Early seizures can develop after homeostatic and systemic disturbances as electrolyte disbalance and acid-base balance. Early seizures are categorized as „acute symptomatic epileptic seizures“ and should be distinguished from genuine epilepsy.

In the present literature we can find different definitions for these conditions, but until now there has been an agreement that early seizures develop within 14 days from the stroke onset, and late seizures after 14th day. The given distribution is important due to different pathophysiological mechanisms that cause these conditions. The most important practical value of this allocation in two categories is the different prognosis, because the most patients with early seizures do not develop late seizures and epilepsy.

Based on the results derived from animal studies, in early seizures (after 2 weeks of ischaemia), patients displayed increased levels of penumbral sodium, intracellular calcium and excitatory glutamate as well as down-regulation of GABAergic inhibition (19, 20). Damaged tissue contains: increased release of excitotoxic glutamate and impairment of the GABA neurons. Epileptic seizures can lead to secondary excitotoxic glutamate damage leading to higher energetic demand in the conditions of ischaemia causing possible irreversible tissue damage. In cases of late seizures, one study reported the disinhibition or development of excitatory axon sprouting and the presence of hemosiderin, gliosis and altered membrane function (21).

Neuronal changes develop in late seizures, the pathogenesis of which is until now not fully understood. The possible reasons for epileptogenesis are: selective neuronal death and apoptosis, membrane changes, mitochondrial changes, receptore changes (for example GABA receptors), deafferentiation and collateral sprouting (at ischaemia site as well as distant places) (22). Penumbra is also considered to contain electrical irritable tissue resembling epileptogenic focus (23).

Experimental studies show that repeated epileptogenic activity in cerebral ischaemia significantly increases the size of the infarct zone and can cause functional worsening of the patient (24).

The incidence of the early epileptic seizures is 2.4–5.4%, and for the late seizures 3–4.5%. In 3.7% epileptic seizures are connected to transitive ischaemic attack (25). It is

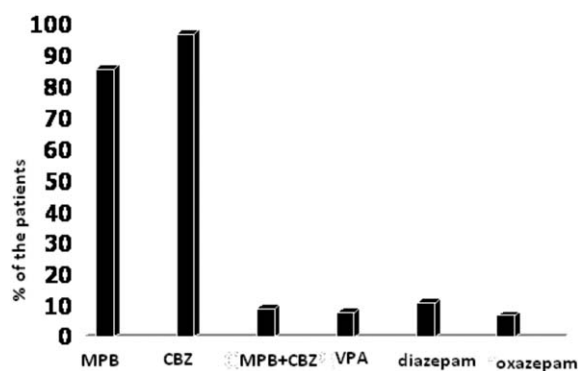


Figure 2. Initial antiepileptic therapy in patients with stroke and epilepsy at the University Department of Neurology, University Hospital Center „Sestre milosrdnice“ hospitalized from 2003–2004. (MPB-methylphenobarbiton, CBZ-carbamazepine, VPA-valproate).

possible that some epileptic attacks are in fact myoclonisms of the extremities within transitive ischaemic attack (TIA) due to the ischaemia in the border zone and do not actually represent epileptic seizures. Between 2.3 and 10.5% of the patients experience single seizure following stroke (21, 26). At 1 year after stroke, the cumulative risk of seizures is 4.2%, mounting to 9.7% after 5 years (27). Transient ischaemic attacks rarely cause epileptic seizures (27).

Although the risk for developing epilepsy was 17–35% after early seizures (1 week after stroke), the risk of developing epilepsy after late seizures increased to 65–90% (29, 30).

Patients exhibiting frontal intermittent rhythmic delta activity and diffuse slowing on post-stroke EEGs have a high risk of developing late onset seizures (31).

COMORBIDITY

The comorbidities in elderly patients with epilepsy and stroke include: psychiatric problems (e.g. depression), sleep disorders (e.g. insomnia), cardiovascular disturbances, cardiac arrhythmias, AV block and hypotonia, osteoporosis, gait disturbances and tremor.

Combination of coronary heart disease, hypertonia and cardiovascular disease occur in 65% of patients over 75 year old (25, 32).

MORTALITY

The standardized mortality rate in patients with epilepsy is double that observed in the healthy population (33). Intrahospital mortality in patients with stroke with epileptic seizures was 37.9% compared to patients without seizures (14.4%). In the first 30 days following acute symptomatic epilepsy, the fatality rate in elderly patients was double that of younger patients (34). It is not known to what size the epileptic seizures themselves represent prognostic factor for the outcome or whether they are only indicator of the severity of stroke. Early seizures cause higher mortality than late seizures which can be explained by synergistic effect of the damaged tissue due to the seizure and vascular ischaemia.

TREATMENT

Acute epileptic seizures in stroke are managed in Intensive care unit in case of epileptic status. Cases of isolated epileptic seizures do not demand antiepileptic therapy.

Retrospective studies have shown that early epileptic seizures do not require longterm antiepileptic therapy for the prevention of subsequent seizure, whereas late seizures require specific antiepileptic treatment (31). Some centers apply AET during 3–6 months after stroke, although the exact period is not determined in the present studies.

It has to be taken into account that the choice of AED depends on: age, severity of stroke, comorbidity and other

drugs taken by patients. Physiological changes in the absorption, distribution, biotransformation, excretion and interaction with other drugs occur with aging. Aging causes changes in the function of several organs that can affect treatment. Reduced liver metabolism and decreased clearance can lead to increased concentrations of AED to even toxic doses (25). Liver volume and mass in elderly patients is up to 20% lower with of the liver metabolism of the AED which are metabolized through cytochrome oxidase, especially seen in carbamazepine, phenytoin, phenobarbitone and valproic acid. As opposed to liver metabolism, decreased kidney clearance is mitigated constantly and predictably. In elderly patients, adverse drug reactions are one of the major limiting factor in patient retention (35). Toxic effect of the AED is manifested as: sedation and behavioral changes (clonazepam, phenobarbitone, primidone), tremor (valproic acid) and hyponatremia (carbamazepine). Although adverse effects have been reported during lamotrigine therapy, these effects occurred more often during treatment with phenytoin and carbamazepine. Of the 10 studies dealing with efficacy and safety of newer antiepileptic drugs since 2000, only one study proved Class 1 evidence (35, 36).

At our department for Neurology we have retrospectively analyzed 1449 patients with epilepsy who were admitted during the year 2003 and 2004. 21.5% of the patients were older than 65 years. Newly diagnosed epilepsy was present in 19,4% of the patients.

Initial antiepileptic treatment was carried out with: methylphenobarbital in 86 patients (30,6%), carbamazepine in 97 patients (34,5%), carbamazepine and methylphenobarbital in 9 patients (3,2%), valproate in 8 patients (2,8%), diazepam in 11 patients (3,9%) and oxazepam in 7 patients (2,5%). Later during follow-up lamotrigine was introduced as monotherapy in 9 patients (3,2%) and in 9 patients as add-on therapy. Topiramate was introduced in 7 patients as monotherapy (2,5%), in 4 patients (1,4%) as add-on therapy. Gabapentin was introduced in 4 patients (1,4%) as monotherapy and in 2 patients (0,7%) as add-on therapy (Fig.2).

US expert rating indicated that the first line drugs to treat epilepsy in the elderly are: lamotrigine, levetiracetam, gabapentin, carbamazepine and oxcarbazepine, which are followed by topiramate and valproate (37). European authors in 2007 indicate that levetiracetam, lamotrigine and gabapentin were first line drugs, followed by topiramate and valproate. Oxcarbazepine and carbamazepine were not highly recommended because of the associated hyponatremia, cardiac disorders and interaction potentials (38).

The potential for drug interaction is extremely important because elderly patients are commonly treated with multiple medications. Carbamazepine, phenytoin, phenobarbital and primidone are strong enzyme inducers, whereas valproate is an enzyme inhibitor. Some AED can slow down recovery from stroke, for example phenytoin in combination with GABA agents (39).

Carbamazepine may influence arterio-ventricular conduction and should not be used in AV block; it can also increase osteoporosis and has considerable interaction potential with warfarin. Valproate can be administered once daily and it has a broad efficacy spectrum against focal and generalized epilepsy. Particular attention must be paid to certain side effects in elderly patients as: encephalopathy, tremor and interactions with anticoagulants. Valproate may increase insidious dementia and Parkinsonian syndrome (40). Gabapentin, pregabalin, levetiracetam, lamotrigine and topiramate do not have any interactions with anticoagulants, however gabapentin, pregabalin and levetiracetam can alter kidney function. Levetiracetam can cause emotional disturbances and topiramate may produce cognitive side effects—especially when used as add on therapy at higher dosages. In monotherapy, topiramate at doses up to 100mg is generally well tolerated. Tremor and insomnia are possible side effects of lamotrigine.

Osteoporosis is common in elderly women and occurs in 15–40% of patients with enzyme-inducing anticonvulsants (41). Carbamazepine, phenobarbitone, phenytoin, primidone and valproate have marked effects on osteoporosis. There is not enough evidence for gabapentin, pregabalin and levetiracetam on osteoporosis, however levetiracetam may reduce bone strength and bone formation without altering bone mass. Lamotrigine monotherapy was not associated with decreased bone density. During treatment with phenobarbital, phenytoin and carbamazepine, gait disturbances were found in 42–55% of the patients older than 65 years (18).

Although lamotrigine, levetiracetam and topiramate have been used with increasing frequency, phenytoin was still the most commonly used AED. In the last decade, there has been a small reduction in the use of phenytoin (from 70 to 66%) and phenobarbital (from 3 to 1%). This reduction is correlated with the increased use of newer antiepileptic drugs (from 12.9 to 19.8%) (39).

The standard antiepileptic drug for focal epilepsy is still carbamazepine, and valproate is most commonly used for generalized epilepsy— even in older patients.

Epidemiological studies on epilepsy treatment in the elderly show steady increase in the number of patients. Therefore, elderly patients require special attention. Monotherapy in low doses is often sufficient, enzyme inducing drug are used too frequently (42, 43).

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