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Late seizures following a first symptomatic brain infarct are related to large infarcts involving the posterior area around the lateral sulcus

LISETTE HEUTS-VAN RAAK*, JAN LODDER* & FONS KESSELS†

**Department of Neurology, University Hospital Maastricht, The Netherlands and †Dept. of Epidemiology, University of Limburg, Maastricht, The Netherlands*

Correspondence to: E. Heuts-van Raak, MD, PhD, Dept. of Neurology, University Hospital Maastricht, P.O. Box 5800, 6202 AZ Maastricht, The Netherlands

Controversies exist concerning factors that contribute to the occurrence of epileptic seizures after stroke. Therefore, we studied prospectively the occurrence of seizures in 322 patients with a first-ever CT-confirmed symptomatic territorial brain infarct involving the cortex. We also studied potential risk factors for seizures, and gave special attention to cortical infarct location. Fifty-four patients developed post-stroke seizures. We distinguished between early- and late-onset seizures, occurring within two weeks following stroke-onset, or later than two weeks, respectively. We found that patients of 65 years or older with a cardioembolic brain infarct involving the middle temporal or post-central gyrus, had an almost eight times increased risk of early-onset seizures, whereas patients with a large brain infarct involving the supramarginal or superior temporal gyrus, had a five times increased risk of late-onset seizures. We conclude that risk factors and epileptogenic cortical areas for post brain infarct seizures can be identified, which however, differ between early- and late-onset seizures. These two seizure types may also differ in terms of seizure mechanism. Our findings may influence the decision on prophylactic treatment with antiepileptic drugs in stroke patients.

Key words: stroke; brain infarct; cortical location; seizures; post-stroke epilepsy.

INTRODUCTION

The frequency of socalled post-stroke epilepsy varies between studies from zero to more than 50%[1–30]. This large variation reflects differences in patient populations studied, study methods, and in the definition of what post-stroke epilepsy signifies. Many studies were retrospective, performed prior to the computed tomography (CT) scan era, or based on small numbers. Also, a distinction between early and late seizures following a stroke was not uniformly made. Such distinction is relevant as early seizures may be related to non-cerebral disarrangements, such as electrolyte imbalance, acid-base disturbances, etc., whereas late seizures may be regarded as 'real' post-stroke epilepsy[26,31]. Furthermore, it remains unclear what factors influence the occurrence of post-infarct seizures, although large infarct size[18,23,29,32,33], (cardio)embolic infarct cause[1,4,6,8,10,31] and haemorrhagic infarction[26,31] may increase the risk. It is generally agreed that cortical involvement is an important risk factor[1,4,18,19,21–26,28,29,31–34], but as in post-traumatic epilepsy, some parts of the brain may be more susceptible to seizure development than others[35–39]. Studies on post-stroke seizures so far mentioned rather large possible epileptogenic brain areas[21,22,32,34,40,41], whereas in post-traumatic epilepsy more discrete areas were identified[35–39]. Earlier, we found the middle temporal, superior temporal, precentral, and supramarginal gyrus frequently involved in epilepsy patients who had prior stroke, but could not exclude that these four middle cerebral artery territory gyri merely reflected a more frequent involvement of this region in brain infarcts in general[42].

Therefore, in a prospective study on brain infarct patients, we registered cortical infarct

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areas on CT in patients who developed post-stroke seizures and those who did not, using a detailed topographical atlas[43].

PATIENTS AND METHODS

Patients were registered between 1 July 1987 and 1 July 1992 in an ongoing prospective register at the University Hospital Maastricht, that includes all adult patients admitted to the Neurological Department or seen at the outpatients' clinic, with a first-ever symptomatic supratentorial brain infarct with symptoms lasting longer than 24 hours. The University Hospital is the only hospital in the Maastricht region with an adherent population of approximately 190 000 people. Patients with a history of former stroke, those with cerebellar or brainstem stroke, primary intracerebral haemorrhage, subarachnoideal haemorrhage, or brain tumor were not included. Brain infarction was defined as the rapid onset of clinical signs of focal cerebral function disturbance, lasting longer than 24 hours or leading to death, with no other apparent cause than that of vascular origin, with normal CT or CT showing an area of low attenuation compatible with the clinical signs and symptoms, or autopsy revealing an infarct compatible with the clinical signs and symptoms[44–46]. When neither CT nor autopsy were available, we used the Guy's Hospital Stroke Diagnostic Score (Allen score)[47] to determine the probability that the stroke was due to infarction. Patients with an Allen score less than four (i.e. with a probability of 90% or more that their stroke was due to infarction) were included in the register[45,47].

All patients were examined as soon as possible after admission or at the first outpatients' clinic visit. In addition to personal data, such as age and sex, clinical infarct syndromes were recorded[45,48,49] and the patient's medical history was reviewed with special attention to prior signs and symptoms of stroke or brain tumor (exclusion criteria), and a history of epileptic seizures. They had routine investigations including standard blood and urine tests, electrocardiography (ECG), chest radiography, non-invasive carotid studies and CT scan. Echocardiography, 24 hour electrocardiographic monitoring (Holter) and cerebral angiography were performed in selected patients.

Cerebral CT scans were independently reviewed by two neurologists without knowledge of the clinical data, except that the patient was in the register. In those patients with a symptomatic infarct on CT, infarct type (lacunar, striatocapsular or territorial), size, location, and whether it was haemorrhagic were determined. The presence of leukoaraiosis was also noted. In case of disagreement on the presence of an infarct or leukoaraiosis CT was regarded as negative for this particular item. Lacunar infarct was defined as a subcortical, small, sharply marginated hypodense lesion in the paraventricular centrum semiovale, the internal capsule or basal ganglia[50], with a diameter of less than 20 mm on CT, most probably due to occlusion of one single perforating artery[45], a striatocapsular infarct as an infarct with a diameter greater than 20 mm on CT, not involving the cortex and not compatible with occlusion of one single perforating artery, and a territorial infarct as a hypodense lesion compatible with a territory supplied by the main stem, or the cortical or medullary branches of one of the three large cerebral arteries. We distinguished large territorial infarcts that involved the entire area supplied by the anterior or posterior cerebral artery, or the complete or larger part of the middle cerebral artery, and infarcts that were smaller, involving only a medium size branch or a small branch area. In addition the affected gyri of all cortical lesions (both the symptomatic and silent infarcts) were identified according to Bories' method[43] allowing a detailed topographical description of cortically-involved areas in different gyri. Three groups of gyri were distinguished that largely comply with the areas compatible with anterior, posterior and middle cerebral artery supply areas. Leukoaraiosis was defined as focal or diffuse hypodensities in the periventricular or deep white matter, not involving the cortex and not compatible with territorial infarction[51,52]. We noted different sites of leukoaraiosis (around the frontal or occipital horn, the centrum semi-ovale, or combinations of these), but here only the presence of leukoaraiosis regardless its extension was used in the analyses.

After reviewing the CT scans, for every patient CT findings were combined with clinical data to determine which infarct on CT was the symptomatic one. An infarct was considered symptomatic if located in the clinically affected hemisphere, in an area that could account for the clinical neurological signs and symptoms, whereas the radiologically estimated age was consistent with the time of clinical symptoms (old lesions being more hypodense, more sharply delineated, or showing signs of retraction of brain structures towards the lesion site). All other visible infarcts not complying with this definition were con-

sidered to be 'silent' brain infarcts. The affected gyri of asymptomatic cortical lesions were included also, because excluding these silent stroke lesions would have left us unable to detect any bias towards an association between such lesions and the occurrence of seizures.

Patients with a symptomatic territorial infarct on CT involving the cortex, and a presumed cardioembolic stroke cause were considered separately. A cardioembolic infarct was defined in patients who had one of the following potential cardiac sources of embolism: chronic or intermittent ECG confirmed atrial fibrillation; left ventricular myocardial infarction within six weeks preceding stroke; left ventricular or atrial thrombus; left ventricular aneurysm; left ventricular akinetic segment; cardiomyopathy; mitral or aortic valve abnormalities (endocarditis, mitral stenosis, prosthetic aortic or mitral valves); and in young patients without any specific stroke cause: atrial septal defect, ventricle septal defect. Remaining patients with a non-cardioembolic symptomatic territorial infarct (presumably large vessel disease, i.e. atherothrombosis or artery-to-artery embolism whether or not confirmed by non-invasive carotid studies) were considered as one group: remaining infarcts.

Follow-up

Follow-up was aimed at every 3–6 months. We paid special attention to the occurrence of epileptic seizures[53] and regarded every seizure occurring after the first symptomatic brain infarct as a post-stroke seizure. As we felt that different seizure types could not always reliably be ascertained, no subdivision as to seizure type was pursued. In the case of an epileptic seizure, date, delay between stroke and first seizure, description of the clinical signs and symptoms, antiepileptic treatment, and possible causes for the seizure (metabolic or electrolyte disturbances, hypoxia or respiratory insufficiency, drug-induced, trauma capitis, subdural haematoma, recurrent stroke) were recorded.

Information on patients discharged to nursing homes was collected by visiting the nursing homes every 6–12 months. Information on patients unable or unwilling to visit the neurological outpatients' clinic, was collected by telephone from the patient or a close relative, from the attending general practitioner, and from reviewing their hospital files. During the first six months of 1993, final follow-up data were gathered, aiming at a follow-up of at least six months for every patient still alive. Duration of follow-up was defined as number of days between stroke and final follow-up contact for patients still alive, and as number of days between stroke and death for deceased patients. Exposure time, expressed as number of days that the patient was at risk for developing post-stroke seizures, was equal to follow-up time for those who did not develop seizures, and was defined as number of days between stroke and first epileptic seizure for the patients who developed post-stroke seizures.

Patient selection

During the five-year intake period 816 patients were registered. Thirteen patients suffered epileptic seizures before their first stroke, two were lost to follow-up very shortly after stroke, and 31 had a variety of 'rare' stroke causes, such as vasculitis, arterial dissection or haematological disorders. These 46 patients were excluded, leaving 770 patients, 737 of whom had CT (96%). Median delay between stroke and CT was 5 days (range, 0–882). In 206 patients (28%), 110 of whom had a cortical syndrome, CT showed no infarct. In 163 patients (22%) CT showed a symptomatic lacunar infarct, in 40 (5%) a symptomatic striatocapsular infarct, and in 328 (45%) a symptomatic territorial infarct involving the cortex. Those 328 patients were eligible for the study, however, six of them (all without seizures) were subsequently excluded: three scans were missing, and three scans only showed space-occupying effect by infarct oedema as an indirect sign of infarction, leaving 322 patients who constituted our final study population.

Statistical methods

After simply counting and comparing the number of patients with seizures in different risk factor subgroups, differences between groups were analysed accounting for differences in exposure time, using Incidence Rate Ratios with 95% confidence intervals (CIs) and two-tailed p-values[54]. In addition the influence of each possible risk factor on the occurrence of post-stroke seizures (dependent outcome variable), was statistically adjusted for differences in the distribution of the other risk factors (explanatory independent variables = covariates) by means of a Cox regression analysis (proportional hazards model), resulting in hazard ratios with 95% CIs and two-tailed p-values.

As early-onset seizures and late-onset seizures may reflect two different underlying epileptic mechanisms with different risk factors, early- and late-onset seizures were analysed separately. As early-onset seizures occurred by definition within two weeks following stroke-onset, in the analyses on early-onset seizures for every patient the maximal exposure time was set at 14 days.

RESULTS

Fifty-four of the 322 patients (17%) experienced one or more epileptic seizures during follow-up, after a median of 199 days (range, 0–1848) between brain infarct and first epileptic seizure. Median follow-up was longer in patients with seizures, 702 days (range, 8–1897) vs. 492 days (range, 1–1998) in those without seizures, biasing the occurrence of seizures towards longer follow-up, because patients with a shorter exposure time are less likely to develop seizures. The percentage of patients who died during follow-up was similar in both groups: 43% (95% CI: 29–56) of patients with seizures and 44% (95% CI: 38–50) of those without died. However, patients without seizures who died, died earlier with a median survival time 81 days (range, 1–1781) vs. 368 days (range, 8–1897) in those with seizures, which explains the difference in median follow-up. By using Incidence Rate Ratios and Cox regression analyses this difference was accounted for. Table 1 shows general features and Fig. 1 the corresponding Incidence Rate Ratios with 95% CIs of patients with, and those without seizures. Patients with seizures were significantly older, had a large infarct significantly more often, whereas their infarcts were significantly more often haemorrhagic. Table 2 shows the affected cortical gyri for both groups. Almost all middle cerebral artery territory gyri were significantly more often affected in patients with seizures, whereas no differences in affected posterior and anterior cerebral artery territory gyri were found.

Early-onset seizures

Fourteen of the 322 patients at risk (4%) experienced their first seizure within two weeks of stroke-onset, after 1.5 days (median; range, 0–14). Tables 1 and 2 show general features and affected cortical gyri for patients with and those without early seizures. Figures 1 and 2 show corresponding Incidence Rate Ratios with 95% CIs. Patients with early seizures were significantly older, had a cause of cardioembolic stroke significantly more often, whereas the middle temporal, inferior temporal, postcentral and angular gyrus were significantly more often affected. As none of the patients younger than 65 years experienced an early seizure, the age limit at 65 years could not be used in the Cox regression analysis. In order not to exclude patients below 65 years, we used

Table 1: General features of patients with and those without seizures following a first-ever supratentorial brain infarct (n = number)

	Any seizures 322 patients are at risk				Early-onset seizures 322 patients are at risk				Late-onset seizures 290 patients are at risk			
	With any seizures $n = 54$		Without any seizures $n = 268$		With early seizures $n = 14$		Without early seizures $n = 308$		With late seizures $n = 41$		Without late seizures $n = 249$	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Age < 65	12	(22)	72	(27)	0		84	(27)	12	(29)	62	(25)
Age 65–75	16	(30)	84	(31)	4	(29)	96	(31)	13	(32)	84	(34)
Age ≥ 75	26	(48)	112	(42)*	10	(71)	128	(42)*	16	(39)	103	(41)
Male sex	26	(48)	140	(52)	6	(43)	160	(52)	21	(51)	131	(53)
Cardioembolic infarct	21	(39)	88	(33)	10	(71)	99	(32)*	11	(27)	79	(32)
Large cortical infarct	27	(50)	85	(32)*	6	(43)	106	(34)	21	(51)	62	(25)*
Haemorrhagic infarct	8	(15)	23	(9)*	3	(21)	28	(9)	5	(12)	21	(8)
Silent cortical lesion	1	(2)	27	(10)	0		28	(9)	1	(2)	24	(10)
Leukoaraiosis	9	(17)	55	(21)	2	(14)	62	(20)	7	(17)	56	(22)
Media-lesion	47	(87)	231	(86)	13	(93)	265	(86)	35	(85)	211	(85)
Posterior-lesion	8	(15)	47	(18)	1	(7)	54	(18)	2	(5)	49	(20)
Anterior-lesion	2	(4)	28	(10)	0		30	(10)	7	(17)	16	(6)

Some patients had infarcts in more than one vascular territory, therefore the total number of media, posterior and anterior lesions exceeds 100%.

* Statistically significant more frequent among patients with seizures; $P < 0.05$.

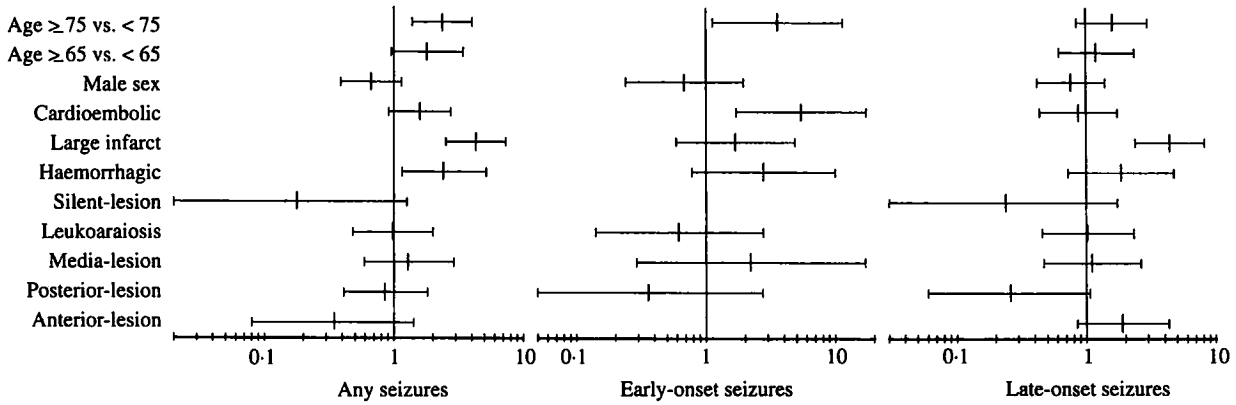

Fig. 1: General features of patients with and those without seizures. Diagram of Incidence Risk Ratios (IRRs) with 95% confidence intervals (CIs) on a logarithmic scale. IRR > 1, increased risk of seizures; 95% CI not including the value 1, difference in risk is statistically significant; $P < 0.05$.

only the age-limit at 75 years, and analysed patients younger than 75 years as one group. Cox regression analysis showed that adjusted for age, sex, haemorrhagic infarction and infarct size, only cardioembolic stroke cause was significantly associated with the occurrence of early seizures:

Table 2: Affected cortical gyri in patients with and those without seizures following a first-ever supratentorial brain infarct (n = number)

	Any seizures 322 patients are at risk				Early-onset seizures 322 patients at risk				Late-onset seizures 290 patients at risk			
	With $n = 54$		Without $n = 268$		With $n = 14$		Without $n = 308$		With $n = 41$		Without $n = 249$	
Affected gyrus	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Middle cerebral artery territory gyri												
Orbital	4	(7)	31	(12)*	1	(7)	34	(11)	3	(7)	12	(5)
Superior temporal	27	(50)	85	(32)*	7	(50)	105	(34)	20	(49)	65	(26)*
Middle temporal	29	(54)	89	(33)*	10	(71)	108	(35)*	20	(49)	72	(29)*
Inferior temporal	9	(17)	40	(15)*	5	(36)	44	(14)*	5	(12)	24	(10)
Middle frontal	10	(19)	49	(18)	2	(14)	57	(19)	8	(20)	27	(11)
Inferior frontal	17	(31)	70	(26)*	5	(36)	82	(27)	12	(29)	51	(20)*
Precentral	28	(52)	117	(44)*	8	(57)	137	(44)	20	(49)	98	(39)
Post-central	31	(57)	116	(43)*	10	(71)	137	(44)*	21	(51)	97	(39)
Supramarginal	36	(67)	126	(47)*	10	(71)	152	(49)	26	(63)	104	(42)*
Occipital lobe	7	(13)	43	(16)*	4	(29)	46	(15)	3	(7)	25	(10)
Angular	18	(33)	74	(28)*	7	(50)	85	(28)*	11	(27)	58	(23)
Sup parietal lobule	4	(7)	35	(13)	1	(7)	38	(12)	3	(7)	16	(6)
Insular cortex	6	(11)	46	(17)	3	(21)	49	(16)	3	(7)	28	(11)
Posterior cerebral artery territory gyri												
Parahippocampal	3	(6)	14	(5)	0		17	(6)	3	(7)	11	(4)
Fusiform	4	(7)	17	(6)	0		21	(7)	4	(10)	14	(6)
Uncus	0		9	(3)	0		9	(3)	0		6	(2)
Occipital lobe	5	(9)	25	(9)	1	(7)	29	(9)	4	(10)	22	(9)
Cingulate	2	(4)	9	(3)	1	(7)	10	(3)	1	(2)	7	(3)
Lingual	3	(6)	22	(8)	0		25	(8)	3	(7)	19	(8)
Cuneus	3	(6)	12	(4)	1	(7)	14	(5)	2	(5)	10	(4)
Precuneus	0		8	(3)	0		8	(3)	0		5	(2)
Anterior cerebral artery territory gyri												
Superior frontal	0		14	(5)	0		14	(5)	0		9	(4)
Rectal	0		6	(2)	0		6	(2)	0		1	(½)
Cingulate	0		10	(4)	0		10	(3)	0		4	(2)
Precuneus	0		13	(5)	0		13	(4)	0		8	(3)
Paracentral lobule	2	(4)	9	(3)	0		11	(4)	2	(5)	7	(3)

* Statistically significant more frequent among patients with seizures; $P < 0.05$.

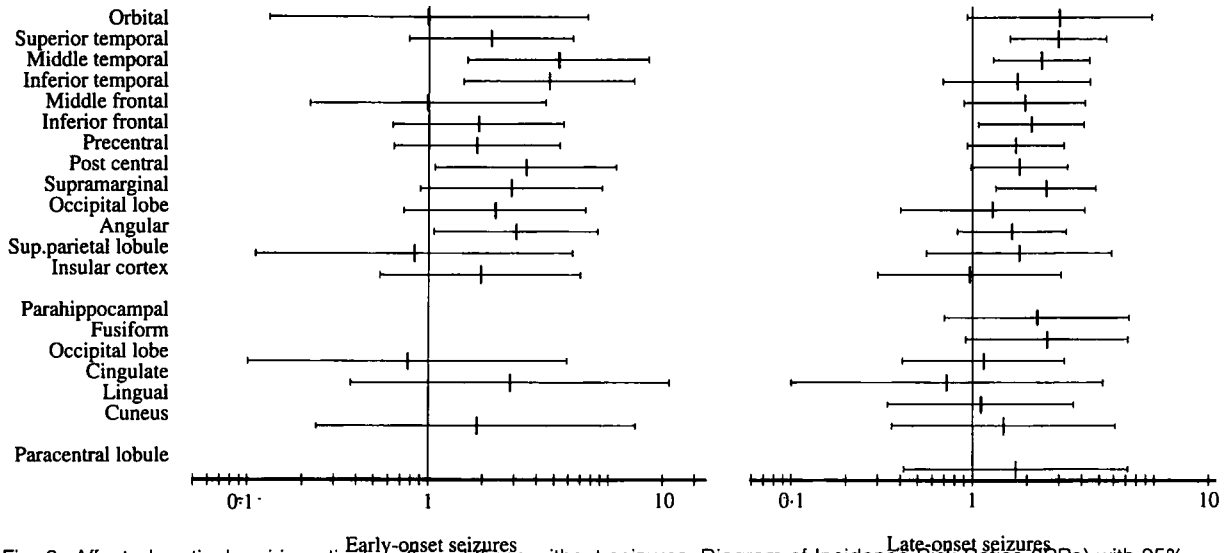

Fig. 2: Affected cortical gyri in patients with and those without seizures. Diagram of Incidence Risk Ratios (IRRs) with 95% confidence intervals (CIs) on a logarithmic scale. IRR > 1, increased risk of seizures; 95% CI not including the value 1, difference in risk is statistically significant; $P < 0.05$.

hazard ratio = 4.07; 95% CI: 1.22–13.52. When, instead of stroke cause, infarct location was added to the model, only the middle temporal gyrus was significantly associated with the occurrence of early seizures: hazard ratio = 4.06; 95% CI: 1.22–13.53. When both stroke cause (cardioembolic vs. remaining infarct) and infarct location were added to the model, beside cardioembolic stroke cause, two gyri were significantly associated with the occurrence of early seizures: the middle temporal gyrus (hazard ratio = 3.38; 95% CI: 1.01–11.34) and the post-central gyrus (hazard ratio = 3.95; 95% CI: 1.04–15.07).

Consequently, patients at risk for developing early seizures were those of 65 years or older with a cardioembolic brain infarct, involving at least the middle temporal or post-central gyrus. Such patients had a risk of early seizures of 13% (95% CI: 5–21), whereas remaining patients had a risk of early seizures of 2% (95% CI: 0–4). The Incidence Rate Ratio for this high risk group is 7.71 (95% CI: 2.58–23.00).

Late-onset seizures

As late-onset seizures occur by definition after two weeks following stroke-onset, 32 patients (10%) who died within these two weeks were not at risk for late-onset seizures and were consequently excluded from the analysis. Of the remaining 290 fourteen-day survivors, 45 patients experienced one or more epileptic seizures later than two weeks following stroke. However, in four of them these were early seizures continuing over the arbitrary limit of two weeks post-stroke. Therefore, we decided to include eventually 41 patients (14%) with 'real' late-onset seizures. Although in four patients the first seizure occurred after a recurrent stroke, in accord with our study aim the first symptomatic brain infarct was used as the index stroke, and these four patients were analysed without taking into account the recurrent stroke.

First late seizure occurred after 274 days (median; range, 18–1848). Tables 1 and 2 show general features and affected cortical gyri for both groups. Corresponding Incidence Rate Ratios with 95% CIs are shown in Figs 1 and 2. Patients with late-onset seizures significantly more often had a large infarct, whereas the superior temporal, middle temporal, supramarginal and inferior frontal gyrus were significantly more often affected. Cox regression analysis showed that adjusted for age, sex, haemorrhagic infarction, asymptomatic lesions, and stroke cause, only large infarct size was significantly associated with the occurrence of late-onset seizures: hazard ratio = 4.68; 95% CI: 2.34–9.39. When infarct location was added to the model instead of infarct size, the superior temporal, middle temporal, supramarginal, middle frontal and inferior frontal gyrus were significantly associated with the occurrence of late-onset seizures: hazard ratio = 2.89; 95% CI: 1.50–5.59; and hazard ratio = 2.31; 95% CI: 1.21–4.40; and hazard ratio = 2.26; 95% CI: 1.17–4.39; and hazard ratio = 2.31; 95% CI: 1.02–5.26; and hazard ratio = 2.04; 95% CI:

1.01–4.14, respectively. When both infarct size and infarct location were added to the model, none of the gyri remained significantly associated with the occurrence of late-onset seizures; only large infarct size remained significant. Therefore, as the middle frontal and inferior frontal gyrus are adjacent areas, the influence of the combination middle frontal and inferior frontal gyrus both being affected was studied, which showed an Incidence Rate Ratio of 2.99 (95% CI: 1.33–6.75). Because the supramarginal, superior temporal and middle temporal gyrus are adjacent areas the combinations supramarginal and superior temporal gyrus both affected, superior temporal and middle temporal gyrus both affected, and supramarginal, superior temporal and middle temporal gyrus all three affected, were studied also, with resultant Incidence Rate Ratios of 4.08 (95% CI: 2.21–7.53); 3.23 (95% CI: 1.69–6.16) and 4.35 (95% CI: 2.28–8.29), respectively. Cox regression analysis with the model without infarct size showed that all these combinations of adjacent gyri were significantly associated with the occurrence of late-onset seizures (middle frontal and inferior frontal gyrus: hazard ratio = 3.37; 95% CI: 1.37–8.28; supramarginal and superior temporal gyrus: hazard ratio = 3.94; 95% CI: 2.02–7.70; superior temporal and middle temporal gyrus: hazard ratio = 2.95; 95% CI: 1.45–6.00; supramarginal, superior temporal and middle temporal gyrus: hazard ratio = 3.90; 95% CI: 1.90–8.02). However, when infarct size was added to the model only the combination supramarginal and superior temporal gyrus both affected remained significantly associated together with large infarct size: hazard ratio = 2.27; 95% CI: 1.02–5.03 and hazard ratio = 2.94; 95% CI: 1.27–6.81, respectively.

Consequently, patients with a first-ever brain infarct at risk for developing late-onset seizures were those in whom both the supramarginal and the superior temporal gyrus were affected, irrespective of stroke cause and infarct size. Their risk of late-onset seizures was 28% (95% CI: 18–38), whereas the remaining patients had a risk of late-onset seizures of 10% (95% CI: 6–14). The Incidence Rate Ratio for this high risk group is 4.08 (95% CI: 2.21–7.53). When infarct size is taken into account, the risk group can be described as: patients with a large brain infarct, that involves at least either the supramarginal or the superior temporal gyrus. Such patients had a risk of late-onset seizures of 29% (95% CI: 18–40), whereas the remaining patients had a risk of late-onset seizures of 10% (95% CI: 6–14). The Incidence Rate Ratio for this high risk group being 5.07 (95% CI: 2.75–9.36).

DISCUSSION

In this prospective study on 322 patients with a first CT-confirmed symptomatic brain infarct involving the cerebral cortex, we found that old age, large infarct size, haemorrhagic infarction, and involvement of certain cortical middle cerebral artery territory gyri all increased the risk of seizures. Reason for including only stroke patients with CT-confirmed infarcts relates to our study aim to investigate infarct characteristics on CT as risk factors for post-stroke seizures. Because patients with a shorter survival are less likely to have seizures, follow-up in patients with seizures was consequently longer. Nevertheless, follow-up in the seizure free group was long enough to develop seizures. In the analyses we accounted for these differences in exposure times.

Early-onset seizures

The high risk group for developing early-onset seizures, with an almost eight times increased risk, were patients of 65 years or older with a cardioembolic brain infarct involving at least the middle temporal or post-central gyrus. Early prophylactic treatment in such patients at high risk for developing early-onset seizures could be considered. However, seizures that occur just after stroke-onset may not be prevented by such treatment.

Late-onset seizures

We found that among the 290 14-day survivors the high risk group, with a four-fold increased risk for developing late-onset seizures, were patients with a brain infarct involving both the supramarginal and the superior temporal gyrus, or patients with a large brain infarct involving at least either the supramarginal or the superior temporal gyrus, in whom such risk is increased five-fold. Prophylactic treatment with antiepileptic drugs even for such high risk groups would appear to be unfeasible, as a rather large number of patients has to be treated to prevent seizures in a relatively small number of them. Treatment after

a first late seizure would therefore be a more preferable policy, but even then advantages and possible drawbacks of antiepileptic drug use in elderly stroke patients should be carefully balanced.

Our results justify the distinction between early- and late-onset seizures, and they confirm the hypothesis that early- and late-onset seizures may differ in terms of seizure mechanism[26,31]. Early seizures may be merely secondary to a variety of disarrangements of non-cerebral factors in the early phase following stroke, such as electrolyte imbalance, acid-base disturbance, and decreased oxygenation by pneumonia, older patients being more sensitive to such disarrangements than young patients. A potential cardioembolic stroke cause increases the risk; cardiac emboli may disintegrate, and reperfusion damage may cause seizures. Such a mechanism probably occurs only shortly after stroke onset. Late-onset seizures may primarily be caused by epileptic disturbances in cerebral 'scars' remaining from large territorial infarcts located in epileptogenic cortical gyri, and may be due to membrane instability of injured brain cells, or disturbances in the GABA-ergic inhibitory system, or in the action of receptors involved in excitatory brain activity, all disturbing the delicate balance between excitatory and inhibitory neural mechanisms in favour of excitation in such 'scarred' brain foci.

Our finding that large infarct size is a risk factor for post-stroke seizures (especially for late-onset seizures) concurs with that of others[18,23,29,32,33], whereas cardioembolic stroke cause only increased the risk of early seizures[31]. However, in contrast with the view of others[26,31] we did not find haemorrhagic infarction on CT to occur more often in the seizure group, or to be an independent predictor of seizures, but this could be related to the low frequency of haemorrhagic infarction in our study. Asymptomatic cortical lesions did not increase or lower the risk of early or late-onset seizures following a brain infarct in the regression analyses, supporting our decision to use the first symptomatic brain infarct as the index stroke in all patients whether or not they had sustained recurrent stroke. We found that the frequency of silent cortical lesions was lower in the seizure group, which may even point at a protective effect.

We found four middle cerebral artery territory gyri significantly more often affected in patients with post-stroke seizures: the middle temporal and post-central gyrus in those with early-onset seizures, and the supramarginal and superior temporal gyrus in those with late-onset seizures. This finding concurs with the results of our earlier retrospective study in epilepsy patients with prior stroke, in whom we found the middle temporal, superior temporal, precentral and supramarginal gyrus more frequently affected[42]. In the traumatic injured brain the lesions with the highest risk of post-traumatic seizures involved the central-parietal region[35–39], according with the general rule 'the closer the (traumatic) lesion to the central sulcus, the greater the possibility of seizure development'[55]. Our data show that this rule does not simply hold true for ischaemic stroke. It is partly true for early seizures, although the temporal area below the superior temporal sulcus was also rather vulnerable. For late-onset seizures, however, the most vulnerable area lies in the temporal region below the lateral sulcus, and in the parietal region above the lateral sulcus; the superior temporal and supramarginal gyrus appear to form an epileptogenic area for late post brain infarct seizures. This difference in risk-regions may indicate that different parts of the brain can be affected by different mechanisms causing hyperexcitation leading to epileptic activity.

We realize that our results apply only to stroke patients with CT-confirmed brain infarcts. Infarct visualization may not only depend on infarct size, but also on the timing of CT: one quarter of clinically diagnosed patients with a cortical syndrome had no infarct on CT. Future MRI studies may further validate the role of certain brain areas in the development of post-stroke seizures.

CONCLUSION

Early- and late-onset seizures represent two different types of epilepsy with specific risk factors and epileptogenic cortical areas: early seizures may merely be secondary to a variety of early non-cerebral disarrangements, especially in older patients, whereas late-onset seizures may be regarded as 'real' post-stroke epilepsy caused by epileptic disturbances in cerebral 'scars' remaining from large territorial infarcts located in epileptogenic cortical gyri.

The risk of developing early seizures is eight times higher in patients 65 years or older with a cardioembolic brain infarct involving the middle temporal or post-central gyrus.

The risk of late-onset seizures is five times higher in patients with a large infarct involving the supramarginal or superior temporal gyrus.

These data may influence treatment decisions in stroke patients.

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