SHORT REPORT

Early epileptic seizures after stroke are associated with increased risk of new-onset dementia

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Background: Subclinical vascular or degenerative lesions occur in the brain before the clinical expression of dementia. Those lesions in a brain that just experienced a stroke may have lower thresholds for early epileptic seizures. Therefore, epileptic seizures may be a marker of subclinical brain lesions, which may lead to dementia.

Objective: To test the hypothesis that patients with stroke who have epileptic seizures without dementia have an increased risk of new-onset dementia.

Methods: 169 consecutive patients with stroke without pre-existing dementia recruited in the Lille Stroke/Dementia Study were investigated (90 men; 150 ischaemic strokes; median age 73 years). Pre-stroke cognitive functions were evaluated with the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), with a cut-off of 104 for the diagnosis of dementia. The patients were followed up over a 3-year period. Dementia was diagnosed with International Classification of Diseases, 10th revision criteria in survivors who underwent neurological visits, and with the IQCODE score in those who could not. The relationship between epileptic seizures and new-onset dementia was studied within 3 years, using life-table methods.

Results: 9 patients (5.3%; 95% CI 2.9 to 8.7%) had early seizures. Epileptic seizures were independent predictors of new-onset dementia within 3 years after stroke (HR 3.81; 95% CI 1.13 to 12.82), with increasing age (HR 1.04; 95% CI 1.01 to 1.08), IQCODE scores at admission (HR 1.08; 95% CI 1.02 to 1.13) and diabetes mellitus (HR 3.52; 95% CI 1.46 to 8.47).

Conclusion: Patients with stroke who have epileptic seizures may be at increased risk of dementia. Whether cognitive follow-up should be systematically performed in those patients remains to be validated.

Hospital-based¹ and population-based² studies have shown that patients with dementia have an increased risk of seizures compared with patients without dementia. We have shown that patients with stroke with pre-existing dementia are more likely to develop seizures.³ However, the influence of early seizures on outcome after stroke is controversial,^{4,5} and no study has evaluated whether epileptic seizures influence the cognitive outcome. Subclinical vascular or degenerative lesions occur in the brain long before the clinical expression of dementia.^{6,7} We hypothesised that epileptic seizures after a stroke is a marker of subclinical lesions in the brain. Therefore, we tested the hypothesis that patients with stroke who have epileptic seizures without dementia have an increased risk of new-onset dementia.

METHODS

We recruited the Lille stroke/dementia cohort over a 28-week period for a prospective evaluation of dementia in patients with stroke.^{7,8} All consecutive patients with stroke (≥ 40 years)

admitted to the stroke unit were eligible, except those with transient ischaemic attack. We excluded patients with pre-existing dementia as defined below. We examined patients according to a standardised procedure, described previously.^{7,8}

Baseline evaluation

We prospectively collected demographic and clinical data, including history of epileptic seizures. We evaluated the severity of the neurological deficits with the Orgogozo's Scale,⁹ which is a 0–100 scale (0 = severe deficit, 100 = no deficit) used in France before the National Institute of Health stroke scale¹⁰ was introduced. We determined on CT scans performed at admission without contrast agents the presence of silent infarcts¹¹ and leucoaraiosis.¹² Cerebral atrophy was evaluated with a visual scale ranging from 0 (no atrophy) to 3 (severe atrophy).^{7,8,13} We determined the location of recent and old strokes using the neuroimaging procedure judged as the most appropriate—that is, either delayed CT scan (87 patients) or MRI scan (82 patients). In all, 33 patients had neither delayed CT nor MRI scan because of death or refusal: in these patients, location of the stroke was determined on the CT scan performed at admission.

Assessment of the pre-existing cognitive state

We assessed the prestroke cognitive state within 48 h of onset of stroke by a French translation of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE).^{14,15} We classified patients with IQCODE scores of ≥ 104 as having pre-existing dementia.¹⁴

Assessment of epileptic seizures

Early seizures were defined according to the guidelines of the International League Against Epilepsy as those occurring within 7 days of onset of stroke.¹⁶ Transient amnesia or isolated and transient changes in the level of consciousness were not classified as seizures.

Follow-up

We evaluated in-hospital mortality. We followed up survivors at month 6, then every year over a 3-year period, by a visit to a neurologist or by telephone contact. For patients seen at the outpatient clinic, we assessed cognitive functions according to a previously reported procedure.⁷ We diagnosed dementia according to the International Classification of Diseases, 10th revision criteria.¹⁷ Impairment in non-verbal memory was required to diagnose dementia in testable patients with aphasia. We obtained, from a close relative, information about the patient's cognitive status as well as an IQCODE score in patients who could not undergo the neuropsychological testing. For patients who could not attend the visit or who died >6 months after the

Abbreviations: IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly

contact, the evaluation of cognitive status was made with the family or general practitioner using the IQCODE.⁷

End point

The end point was the occurrence of new-onset dementia before month 36.

Ethics

The study protocol was approved by the ethical committee of the Lille University Hospital, Lille, France.

Statistical analysis

After exclusion of patients with pre-existing dementia, we evaluated the relationship between epileptic seizures and new-onset dementia within 3 years after stroke with a Kaplan–Meier analysis (log-rank test), and studied independent predictors of new-onset dementia within 3 years after stroke with a Cox proportional hazard model. Only variables with p value <0.2 in the bivariate analysis were considered for multivariate analysis. Cerebral atrophy was not included in the multivariate model because of colinearity with age. The statistical analyses were computed using SPSS V.11.5.

RESULTS

Study population

The study population consisted of 169 consecutive patients with stroke with an IQCODE score <104 (90 men; median age 73 years, ranging from 42 to 100 years; 150 ischaemic strokes). We considered stroke location as undetermined in 24 patients: 13 patients had no delayed imaging and stroke was not visible on the first CT scan, and 11 patients had no visible lesion on delayed imaging. No survivor was lost to follow-up at month 36.

Nine patients (5.3%; 95% CI 2.9 to 8.7) developed epileptic seizures. Their median age was 75 (range 43–89) years: three of them had an intracranial haemorrhage, and six an infarct; in six patients, seizures occurred within the first 24 h after stroke onset. We classified epileptic seizures as simple partial in three

patients, one of which was secondarily generalised, and as generalised tonic-clonic without sign of focal onset in four patients. One patient had an initial partial status epilepticus, and the type of seizure could not be defined with certainty in one patient. Among the 9 patients with early seizures, 4 (44%) were treated (2 with carbamazepine, 2 with valproic acid).

During the follow-up, 65 (38.5%) patients died: 27 at the acute stage, 15 between discharge and the month 6 visit, 10 between month 6 and month 12, 6 between month 12 and month 24, and 7 between month 24 and month 36.

Thirty six patients (median age at stroke onset 76 years) developed new-onset dementia (21.3%; 95% CI 15.1 to 27.5). Among them, 16 (44.4%) died within 3 years.

Relationship between epileptic seizures and cognitive outcome

Among the 169 patients, those who had epileptic seizures were more likely to develop new-onset dementia during the follow-up: the cumulative proportion of survivors without dementia at the end of follow-up was 72.8% in patients without epileptic seizures and 40% in patients with epileptic seizures ($p = 0.05$). Table 1 shows in detail the other results of the bivariate comparison between patients with and without epileptic seizures. The Cox proportional hazard model found that epileptic seizures were independent predictors of new-onset dementia within 3 years (hazard ratio (HR) 3.81; 95% CI 1.13 to 12.82), besides increasing age (HR 1.04; 95% CI 1.01 to 1.08), Orgogozo's score at admission (HR 0.98; 95% CI 0.97 to 0.99), IQCODE scores at admission (HR 1.08; 95% CI 1.02 to 1.13) and diabetes mellitus (HR 3.52; 95% CI 1.46 to 8.47) (table 2).

DISCUSSION

Our study suggests that patients with stroke with epileptic seizures have an increased risk of new-onset dementia within 3 years after stroke.

This is to our knowledge the first study which focused on the relationship between epileptic seizures and the cognitive outcome after stroke. Cognitive decline was carefully evaluated

Table 1 Factors associated with the risk of new-onset dementia within 3 years after stroke

Demographic data	Male	Female	p Value
Sex	71.5	71.6	0.91
Age (years)	≤ 6	>6	
Level of education	79.4	78.5	0.7
Medical history	Yes	No	
Previous stroke or TIA	58.9	75.2	0.09
Alcohol misuse	78.6	69.5	0.39
Diabetes	46.2	74.3	0.01
Type of stroke	Ischaemic	Haemorrhagic	
	70.5	81.8	0.45
Stroke aetiology (ischaemic only)	Yes	No	
Atherosclerosis	81.3	70.1	0.49
Cardioembolism	52.6	75.7	0.04
Small-vessel occlusion	74.5	70.6	0.56
Other definite cause	100	78.2	NA
Undetermined cause	70.7	72.1	0.32
Location of the lesions (old and new)	Yes	No	
Superficial	64.8	74.5	0.35
Deep	68.2	78.9	0.21
Posterior fossa	77.8	70.5	0.53
Occurrence of seizures	Yes	No	
Early seizures	40	72.8	0.05

NA, not applicable; TIA, transient ischaemic attack.

Results of the bivariate analysis for qualitative variables (Kaplan–Meier method: log-rank test). Numbers are the cumulative proportion of patients without dementia at the end of the study (%).

Table 2 Factors associated with new-onset dementia within 3 years after stroke

Variable	HR (95% CI)
Age*	1.05 (1.02 to 1.08)
IQCODE's score†	1.08 (1.04 to 1.13)
Orgogozo's score at admission†	0.98 (0.97 to 0.99)
Cerebral atrophy score†	2.27 (1.59 to 3.24)
Leucoaraiosis score†	1.68 (1.25 to 2.25)

IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly. Results of bivariate analysis for quantitative variables (Cox model).

*For 1-year increase.

†For 1-point increase.

before the stroke, explaining why we could exclude patients with pre-existing dementia and identify those with new-onset dementia. We hypothesised that epileptic seizures are a marker of an underlying condition that is associated with an increased susceptibility to dementia. It may be due to (1) a more severe underlying vascular pathology, (2) an underlying preclinical degenerative disease such as Alzheimer's disease or (3) complications which may induce seizures or show a slight cognitive decline. Theoretically, pre-existing vascular pathologies that may predispose to both epileptic seizures and new-onset dementia could be white matter changes,¹⁸ silent infarcts⁷ or microbleeds,¹⁹ as these factors are frequent in both stroke and dementia. Those subclinical lesions may not be identified on CT scan or conventional MRI. Moreover, the Cox model showed that diabetes mellitus is a risk factor for dementia. This has previously been shown^{20, 21} and might account for some effects due to subclinical brain damage not seen on CT scans. Larger studies are necessary to provide more information on the link between epileptic seizures and new-onset dementia.

Experimental studies in rats suggest that repeated seizure-like activity in the setting of cerebral ischaemia increases infarct size and can impair functional recovery.²² However, if repeated seizures are undoubtedly harmful, it is not clear whether a single seizure may also lead to a worse outcome after brain injury, and especially to a worse cognitive outcome.

Although it would be clinically valuable to have some ideas about electroencephalographic activity in patients with stroke and their possible predictive value, our study was not designed to study that point. In the light of recent studies,^{23, 24} continuous EEG in the acute phase may help to identify patients at risk for poor outcome.

The weakness of our study is the small number of epileptic seizures. Conclusions should be confirmed in a larger cohort. However, the results are statistically significant and we performed survival analyses. Data were prospectively collected, no patient was lost to follow-up, all seizures were carefully recorded, the IQCODE was used to identify pre-existing dementia and chose a cut-off of 104 to prevent overestimation of dementia.¹⁵ The incidence rate of epileptic seizures was 5.3%, which is similar to figures reported previously,²⁵ suggesting that our population and methods did not differ from those of other studies, and did not influence our results.

In conclusion, patients with epileptic seizures after stroke may have an increased risk for new-onset dementia. Whether patients with epileptic seizures should be carefully followed up for the occurrence of new-onset dementia that may require a specific management should be studied.

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