Brief Report

Incidence and Predictors of Late Seizures in Intracerebral Hemorrhages

Costanza Rossi, MD, PhD; Veerle De Herdt, MD, PhD; Nelly Dequatre-Ponchelle, MD; Hilde Hénon, MD, PhD; Didier Leys, MD, PhD; Charlotte Cordonnier, MD, PhD

Background and Purpose—To identify incidence and predictors of late seizures (LS, occurring >1 week of stroke) in a cohort of patients with intracerebral hemorrhage (ICH).

Methods—Prospective cohort of consecutive adults with spontaneous ICH. Incidence and predictors were identified with Cox regression. We included multivariate analyses on MRI biomarkers (global cortical atrophy, leukoaraiosis, brain microbleeds).

Results—Our study population consisted of 325 patients: 54% men, median age 70 years (interquartile range, 59–78). During 778 person-years of follow-up, the incidence rate was 4 new cases/100 person-years (95% confidence interval, 3–6). The median delay between ICH and LS was 9 months (interquartile range, 3–23). The only factor independently associated with the occurrence of LS was a cortical involvement of the ICH (hazard ratio, 2.8; 95% confidence interval, 1.3–6.1). Concerning MRI biomarkers, multivariate analyses found lobar brain microbleeds to be associated with LS (hazard ratio, 2.4; 95% confidence interval, 1.1–5.4), especially if ≥3 (hazard ratio, 2.7; 95% confidence interval, 1.1–6.8). LS were associated with a worse functional outcome after 3 years of follow-up (P=0.009).

Conclusions—LS frequently occur >9 months after ICH onset, imposing a long-term follow-up. The association of lobar brain microbleeds with the risk of LS might suggest a link with the underlying vasculopathy (cerebral amyloid angiopathy). (Stroke. 2013;44:00-00.)

Key Words: cerebral amyloid angiopathy ▪ intracerebral hemorrhage ▪ seizures ▪ stroke

Data on intracerebral hemorrhage (ICH)-related seizures are scarce and often come from mixed cohorts with a reported incidence of 4% to 16%. We previously reported a 14% incidence of early seizures (ES), which were associated with cortical involvement of the ICH and did not influence in-hospital mortality or outcome at 6 months. However, their influence on the risk of developing late seizure (LS) remains uncertain.

Our aim was to identify the incidence and predictive factors of LS in patients with a spontaneous ICH.

Patients and Methods

The Prognosis of InTra-Cerebral Hemorrhage cohort is an ongoing observational study. We prospectively recruited all adults admitted to the emergency department of Lille University Hospital for a stroke related to spontaneous ICH (from November 2004 to April 2009).

Seizures were defined according to the International League Against Epilepsy criteria and classified as focal or generalized. We recorded dates of seizure incidence and distinguished as ES ≤7 days and LS >7 days after stroke. Use of antiepileptic drugs was recorded.

The original cohort consisted of 562 patients. Patients who had a history of seizures before stroke (n=36), for whom the occurrence of previous seizures was unknown (n=4) and who died within the first 7 days of stroke (n=197), were excluded. We prospectively collected clinical data and medical history, including vascular risk factors. Computed tomographic scans were performed at admission in all patients. Lesions were considered to be cortical when they involved cortical areas, even if the origin of the bleeding was in deep structures.

Concerning MRI biomarkers, brain microbleeds (BMB) were counted throughout the brain. BMB located in the cortex, in the gray-white matter junction and in the subcortical white-matter, were considered as lobar. We evaluated the severity of global cortical atrophy and leukoaraiosis.

Patients were invited to be followed up at 6 months, then annually. At each visit, the occurrence of seizures (dates of seizures were ascertained from medical reports and interviews) and treatments were recorded.

Statistical Analyses

We performed survival analysis using life tables, Kaplan–Meier statistics, and Cox models, starting at the date of ICH presentation, and censoring on the date of first LS, of death, or end of follow-up. To identify predictors of LS, we performed multivariate analyses (Cox...
Table 1. Factors Associated With Late Seizures

<table>
<thead>
<tr>
<th></th>
<th>All Patients (n=325)</th>
<th>LS (n=31)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>176 (54)</td>
<td>14 (45)</td>
<td>0.196</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>206 (63)</td>
<td>16 (52)</td>
<td>0.116</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>48 (15)</td>
<td>7 (22)</td>
<td>0.163</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>102 (31)</td>
<td>7 (22)</td>
<td>0.136</td>
</tr>
<tr>
<td>Excessive alcohol consumption</td>
<td>81 (25)</td>
<td>10 (32)</td>
<td>0.669</td>
</tr>
<tr>
<td>Smoking</td>
<td>61 (19)</td>
<td>8 (26)</td>
<td>0.463</td>
</tr>
<tr>
<td>Previous stroke/TIA</td>
<td>58 (18)</td>
<td>5 (16)</td>
<td>0.885</td>
</tr>
<tr>
<td>Previous AF</td>
<td>32 (10)</td>
<td>3 (10)</td>
<td>0.859</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>44 (13)</td>
<td>5 (16)</td>
<td>0.545</td>
</tr>
<tr>
<td>Cortical involvement</td>
<td>116 (36)</td>
<td>19 (61)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Early seizures</td>
<td>51 (16)</td>
<td>8 (26)</td>
<td>0.102</td>
</tr>
<tr>
<td>Age, y*</td>
<td>70 (58–79)</td>
<td>65 (51–76)</td>
<td>0.145</td>
</tr>
<tr>
<td>NIHSS (admission)*</td>
<td>10 (4–18)</td>
<td>10 (5–21)</td>
<td>0.057</td>
</tr>
<tr>
<td>Volume ICH, mL*</td>
<td>10.2 (9.2–27.5)</td>
<td>20 (8–34)</td>
<td>0.016</td>
</tr>
<tr>
<td>MRI data</td>
<td>n=231</td>
<td>n=26</td>
<td></td>
</tr>
<tr>
<td>Lobar Brain microbleeds*</td>
<td>0 (0–2)</td>
<td>0 (0–5)</td>
<td>0.07</td>
</tr>
<tr>
<td>Global cortical atrophy*</td>
<td>2 (1–2)</td>
<td>2 (1–2)</td>
<td>0.6</td>
</tr>
<tr>
<td>Leukoaraiosis*</td>
<td>1.5 (1–2.5)</td>
<td>1.25 (1–2.5)</td>
<td>0.2</td>
</tr>
<tr>
<td>Functional outcome at 3 years</td>
<td>n=154</td>
<td>n=19</td>
<td></td>
</tr>
<tr>
<td>mRS≥3</td>
<td>64 (41)</td>
<td>13 (68)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Results of bivariate analyses. Data are numbers (%). Analysis: Kaplan–Meier, log-rank test. Unless specified * (Cox models for continuous variables); median (interquartile range) for description only.

AF indicates atrial fibrillation; ICH, intracerebral hemorrhage; mRS, modified Rankin Score; NIHSS, National Institute of Health Stroke Scale; and TIA, transient ischemic attack.

We also analyzed (Cox models) the possible predictive role of BMB defined as total number, BMB in lobar location, severity of lobar BMB (0=reference, 1–2, and ≥3), and cortical involvement (0=reference, 1–2, and ≥3). We applied 4 models as follows: each MRI biomarker was entered univariately (model 1); adjusted for age and sex (model 2); adjusted for model 2 and cortical involvement (model 3); and adjusted for model 3, global cortical atrophy, and leukoaraiosis (model 4).

The influence of LS on functional outcome (mRS≥3 after 3 years of follow-up) was evaluated with Kaplan–Meier statistics.

Detailed methods are provided in the online-only Data Supplement.

Table 2. Risk Estimates of Late Seizures

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total BMB 0–1</td>
<td>1.3 (0.6–3.0)</td>
<td>1.6 (0.7–3.6)</td>
<td>1.8 (0.7–4.2)</td>
<td>2.8 (1.1–7.7)*</td>
</tr>
<tr>
<td>Lobar BMB 0–1</td>
<td>2.0 (0.9–4.4)</td>
<td>2.4 (1.1–5.4)*</td>
<td>2.4 (1.01–5.4)*</td>
<td>3.9 (1.5–10.3)*</td>
</tr>
<tr>
<td>Lobar BMB per category</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>(reference)</td>
<td>(reference)</td>
<td>(reference)</td>
<td>(reference)</td>
</tr>
<tr>
<td>1–2</td>
<td>1.8 (0.7–4.6)</td>
<td>2.1 (0.8–5.7)</td>
<td>2.1 (0.7–5.6)</td>
<td>3.3 (1–9.5)*</td>
</tr>
<tr>
<td>≥3</td>
<td>2.2 (0.9–5.5)</td>
<td>2.7 (1.1–6.8)*</td>
<td>2.7 (1.1–6.8)*</td>
<td>5.8 (1.6–21.2)*</td>
</tr>
</tbody>
</table>

Overall population with MRI (n=231). Analysis: Cox proportional hazard model.

Model 1: uncorrected model; model 2: adjusted for age and sex; model 3: adjusted for model 2 and cortical involvement; model 4: adjusted for model 3, global cortical atrophy, and leukoaraiosis. Numbers are hazard ratio (confidence interval). BMB indicates brain microbleeds.

Discussion

We found an incidence of LS of 4 new cases/100 person-years (95% CI, 3–6) in a cohort of ICH with a strong influence of cortical involvement. Among MRI biomarkers, the presence of lobar microbleeds (HR, 2.4; 95% CI, 1.0–5.4; P=0.04), whereas total BMB did not predict LS. The predictive effects of lobar BMB remained significant after adjustment for severity of global cortical atrophy and leukoaraiosis, with a strong impact of number of lobar BMB (≥3 BMB; Figure). The occurrence of LS was associated with a worse functional outcome (mRS≥3) after 3 years of follow-up (P=0.009).

MRI Biomarkers

Two hundred thirty-one patients (median age, 68 years [interquartile range, 56–78]) underwent MRI (Table 2). Cox models showed that lobar BMB were predictors of LS, after adjustment for age, sex, and cortical involvement of ICH (HR, 2.4; 95% CI, 1.0–5.4; P=0.04), whereas total BMB did not predict LS. The predictive effects of lobar BMB remained significant after adjustment for severity of global cortical atrophy and leukoaraiosis, with a strong impact of number of lobar BMB (≥3 BMB; Figure).

The occurrence of LS was associated with a worse functional outcome (mRS≥3) after 3 years of follow-up (P=0.009).

The cohort consisted of 325 patients (54% males, median age 70 years, interquartile range 58–79).

During 778 person-years of follow-up (median follow-up, 2.2 years [interquartile range, 0.97–4.31]), 31 patients developed ≥1 LS, resulting in an incidence rate of 4 new cases/100 person-years (95% confidence interval [CI], 3–6). The median delay between ICH and LS was 9 months (interquartile range, 3–23).

Bivariate analyses are presented in Table 1. In multivariate analysis, the only factor independently associated with the occurrence of LS was a cortical involvement of the ICH (hazard ratio [HR], 2.8; 95% CI, 1.3–6.1; P=0.01).

ES were not predictors of LS (HR, 1.9; 95% CI, 0.9–4.3; P=0.1). Among 51 patients with ES, the risk of developing LS did not significantly differ between patients treated with long-term antiepileptic drugs and those without long-term antiepileptic drugs treatments (HR, 1.4; 95% CI, 0.4–5.6; P=0.6).
MRI, highlighting limitations to the sample size attributable to monocentric recruitment.

In our cohort, ES did not predict the risk of developing LS. Data in the literature are scarce and mainly come from cohorts that gathered infarcts and ICH.9 In line with our results, the largest ICH study also found that ES were not predictive of LS.10 Interestingly, patients with LS had a worse functional outcome, suggesting that LS may either have a direct influence on outcome or may simply be symptomatic of the severity of the underlying disease.

Our main finding is the association between lobar microbleeds and the occurrence of LS during long-term follow-up. The number of lobar BMB (≥3) was also important, even if there is no clear threshold like in other disease settings.11 The association between lobar BMB and the risk of LS might suggest a link with the underlying vasculopathy (cerebral amyloid angiopathy).12 Future prospective studies on larger cohorts of patients with ICH are warranted to confirm these findings.

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Supplemental Methods
Late seizures in intracerebral hemorrhages

STROKE/2012/000232R2

Rossi C et al.

Patients and Methods

Inclusion and exclusion criteria

The Prognosis of InTra-Cerebral Hemorrhage (PITCH) cohort is an ongoing observational study. We recruited prospectively from November 2004 until April 2009 data of all adults admitted to the emergency department of Lille University Hospital for an acute stroke, who had a parenchymal hemorrhage on the CT scan performed at admission\(^1\). The patients were included irrespective of the clinical severity and of the specialist in charge of the patient. We did not include patients who had, at admission or during follow-up, clear evidence of an underlying cause of Intracerebral Hemorrhage (ICH) such as intracranial vascular malformation, head trauma, tumor or hemorrhagic transformation within an infarct. Pure intra-ventricular hemorrhages were not included. We did not recruit patients referred from other hospitals: our inclusion criteria were designed to evaluate our recruitment as a primary care centre only. The main baseline characteristics of patients included in the PITCH cohort are close to those of ICH patients recruited in the population-based Dijon stroke registry, indicating a good external validity, in line with recommendations for observational studies\(^2\).

Evaluation of seizures

The original population of the cohort consisted of 562 patients. Patients who had history of seizures before stroke (n=36) or patients for whom the occurrence of previous seizures was not known (n=4) were excluded. Because of Late Seizures (LS) definition, patients who died within the first seven days (n=197) were excluded. Therefore, the present study population consisted of 325 patients.

Seizure ascertainment was based on clinical diagnosis. Seizures were defined according to the International League Against Epilepsy (ILAE) as a paroxysmal disorder of the central nervous system with or without loss of consciousness or awareness, and with or without motor involvement. Seizures were classified as focal or generalized (including partial seizures with secondary generalization).

We recorded the dates of seizure occurrence and distinguished: (i) Early Seizures (ES) as those occurring within 7 days of stroke (including onset seizures); and (ii) LS as those occurring beyond one week of stroke as recommended by the ILAE guidelines\(^3\). Use of antiepileptic drugs (AEDs) was systematically recorded and was left to the opinion of the treating physician.

Clinical data at admission and medical history

We prospectively collected the following demographic characteristics: age, gender, vascular risk factors according to the medical history provided by the patient, family or general practitioner as previously described. We recorded history of previous stroke (ischemic or hemorrhagic) or transient ischemic attacks, ischemic heart disease, atrial fibrillation, arterial hypertension, diabetes mellitus, dyslipidemia, excessive alcohol consumption and smoking. We recorded also the occurrence of ES.

We evaluated the severity of the neurological deficit by the National Institute of Health Stroke Scale (NIHSS)\(^4\) and monitored the in-hospital death rate.

Radiological assessment

Computed tomography scans were performed at admission in all patients with continuous slices, no gap, 3 mm slice thickness in the posterior fossa and 5 mm in the hemispheres. The location of the ICH was considered for unique ICH only: (i) lobar (frontal, temporal, parietal and occipital) when the origin of the hemorrhage appeared to be in the cerebral hemispheres...
Late seizures in intracerebral hemorrhages \textbf{STROKE/2012/000232R2} Rossi C et al.

superficial to the deep grey matter structures; (ii) deep when originating from lenticular or caudate nuclei, thalamus, internal or external capsule and (iii) in the posterior fossa when originating from the brainstem or cerebellum. The location was considered undetermined in cases of large intracerebral hemorrhage when the origin could not be reliably identified. In few cases, ICH location was not determined because of simultaneous bleeding in different parts of the brain. Lesions were considered to be cortical when they involved cortical areas, even if the origin of the bleeding was in deep structures, even in patients with multiple bleeding. We calculated the volume of the ICH according to the AXBXC/2 method\textsuperscript{5}.

In patients without contra-indication, Magnetic Resonance Imaging (MRI) was performed. All MRI scans were performed on a Philips 1.5-Tesla machine. Among other sequences, we used for the present study the following sequences (axial orientation): fluid-attenuated inversion recovery (TR, 11000; TE, 140; matrix, 240×119; FoV, 240; slice thickness, 5 mm; slice gap, 1 mm; NEX, 2); gradient echo T2* (TR, 11000; TE, 140; FoV, 240; matrix, 240×119; slice thickness, 5 mm; slice gap, 1 mm; NEX, 3).

We defined brain microbleeds (BMB) as round lesions with low signal on T2*-weighted images within the brain parenchyma (diameter <10 mm). BMB were rated using the BOMB scale\textsuperscript{6}. According to this scale, BMB located in the cortex, in the grey-white matter junction and in the subcortical white matter were considered as lobar. All the other locations (basal ganglia grey matter, internal/external capsule, thalamus, brain stem, and cerebellum) have been classified as non lobar. The total number of BMB was counted. For the present study, we considered definite BMB only as described in the BOMB scale.

We also evaluated the severity of the Global Cortical Atrophy (GCA) (range, 0–3)\textsuperscript{7} and severity of leukoaraiosis (range, 0–3)\textsuperscript{8}.

Images were reviewed in the Digital Imaging and Communications in Medicine (DICOM) format by a study investigator (H.H.) who is a senior stroke specialist trained in neuroradiology and who was blinded to the clinical data and not involved in the management of the patients. BMB were rated by another study investigator (C.C.) who is a senior stroke specialist with expertise in BMB rating.

\textit{Follow-up}

Patients were invited to be followed-up at 6 months, then annually as part of our routine follow-up of stroke patients. At each visit the occurrence of seizures, recurrent stroke (ischemic or hemorrhagic) or Transient Ischemic Attack (TIA) and treatments were recorded. The date of seizures was ascertained from multiple sources: (i) interviews from patients, relatives and general practitioner, (ii) medical reports from our institution or others. Those who were not able to attend the outpatient clinic were interviewed and data were completed by their general practitioner or physician in charge (in case of patients who were still in rehabilitation centers). A few patients were lost to follow-up.

\textit{Ethics}

The study protocol was considered as observational by the internal review board of the Lille University Hospital. The database was declared to the ad hoc commission protecting personal data.

\textbf{Statistical analyses}

\textit{Overall cohort}
Late seizures in intracerebral hemorrhages

We performed survival analysis using life tables and Kaplan-Meier statistics, starting at the date of ICH presentation, and censoring on the date of first LS, date of death or at the end of follow-up if an event of interest did not occur.

The predictors of LS were identified using the log rank test for categorical variables and the Cox proportional hazards analysis for continuous variables.

We pre-specified the variables for the multivariate analyses based on p value ≤0.1 in the bivariate analysis. Multivariate analyses were performed using the Cox proportional-hazards analysis including ES, cortical involvement of the ICH, and ICH volume. ICH volume and NIHSS score were strongly correlated with each other. Therefore we only introduced ICH volume in the multivariate model.

**MRI biomarkers**

We analyzed BMB in 3 ways. We evaluated (i) the presence versus absence of BMB throughout the brain, (ii) the presence versus absence of BMB in lobar location, (iii) the predictive effects of the severity of lobar BMB defined as a categorical variable (0= reference, 1 or 2 BMB, and 3 or more BMB). To estimate the risk of LS associated with the MRI markers, Cox proportional hazards models were used. We built our models according to pre-specified variables gathered from scientific rationale (e.g. cortical ICH location and lobar microbleeds; age and microbleeds, etc.) and previous published study (e.g. global cortical atrophy and leukoaraiosis).

The influence of LS on functional outcome was measured with the modified Rankin Score (mRS) after 3 years of follow-up; we considered as dependent patients with a mRS≥3. We performed survival analysis using Kaplan-Meier statistics.

Statistical analyses were performed using SPSS version 15.0.
Late seizures in intracerebral hemorrhages

References


3. Guidelines for epidemiologic studies on epilepsy. Commission on epidemiology and prognosis, international league against epilepsy. Epilepsia. 1993;34:592-596


