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What are the causes of pre-existing dementia in patients with intracerebral haemorrhages?

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In intracerebral haemorrhage, the most frequent underlying vasculopathies are cerebral amyloid angiopathy and hypertensive vasculopathy. Although both are associated with cognitive impairment, no study has focused on pre-existing dementia in patients with intracerebral haemorrhage. Therefore, we aimed to determine prevalence and mechanisms of pre-existing dementia in a large cohort of patients with an intracerebral haemorrhage. In a cohort of 417 patients, we evaluated the cognitive status before intracerebral haemorrhage with the Informant Questionnaire on Cognitive Decline in the Elderly. The cut-off to diagnose cognitive impairment with no dementia was 53 and 64 for pre-existing dementia. We determined factors associated with pre-existing dementia in multivariate analyses in the overall cohort and among patients with lobar only or deep only intracerebral haemorrhages. We performed post-mortem examinations when possible. Of 417 patients (median age 72 years, interquartile range 58–79), 58 (14%; 95% CI 11–18%) patients had cognitive impairment with no dementia and 65 had pre-existing dementia (16%; 95% CI 12–19%). In lobar intracerebral haemorrhage, the prevalence was 23%, and factors associated with pre-existing dementia were increasing age (odds ratio: 1.09 per year; 95% CI 1.02–1.15), having <8 years of education (odds ratio: 8.37; 95% CI 1.91–36.65) and increasing cortical atrophy (odds ratio: 3.34 per step; 95% CI 1.40–7.96). The five autopsied patients had Alzheimer's disease with cerebral amyloid angiopathy. In deep intracerebral haemorrhage, factors associated with pre-existing dementia were presence of old territorial vascular lesions (odds ratio: 4.52; 95% CI 1.18–17.42) and increasing severity of leucoaraiosis (odds ratio: 4.11 per step; 95% CI 1.73–9.75); the autopsied patient had small-vessel disease without Alzheimer's disease. These findings support the fact that pre-existing dementia is frequent in patients with intracerebral haemorrhage and may be the consequence of two different mechanisms: neurodegeneration with Alzheimer's disease and cerebral amyloid angiopathy in lobar intracerebral haemorrhage versus vascular process in deep intracerebral haemorrhage. These findings may contribute to the improvement of prevention and management of patients with intracerebral haemorrhages.

Introduction

Stroke and dementia are closely related. About 1 in 10 patients have dementia before their first stroke, 1 in 10 develop new dementia after their first stroke and more than one in three develop dementia after a recurrent stroke (Pendlebury and Rothwell, 2009). Although the prevalence of pre-existing dementia and its impact on outcome has been described previously, the underlying mechanisms remain debated. The association with previous stroke, vascular risk factors and vascular lesions on imaging would suggest a vascular origin, while medial temporal lobe atrophy, female gender and a family history of dementia would suggest an important role for a neurodegenerative process (Hénon *et al.*, 1997; Pendlebury and Rothwell, 2009).

In patients with intracerebral haemorrhage, the most frequent underlying vasculopathies are cerebral amyloid angiopathy and hypertensive vasculopathy, both associated with cognitive impairment, either of vascular (Bowler and Gorelick, 2007) or of Alzheimer (Jellinger and Attems, 2003) types. However, most of our knowledge of pre-stroke dementia relies on cohorts that only or prominently included ischaemic strokes. Only three cohorts have reported data on pre-existing dementia in a small subgroup of patients with intracerebral haemorrhage using a systematic and standardized questionnaire (Hénon *et al.*, 1997; Barba *et al.*, 2001; Klimkowicz *et al.*, 2004). Therefore, the available literature on pre-existing dementia in patients with intracerebral haemorrhage relies on only 117 patients without autopsy data.

Our objective was to study prevalence and presumed causes of pre-existing dementia in a cohort of patients with intracerebral haemorrhage. We hypothesized that the cause of pre-existing dementia differs according to the location of the intracerebral haemorrhage, i.e. to the underlying cause of the intracerebral haemorrhage, with a prominence of vascular causes in deep intracerebral haemorrhage and of Alzheimer's disease or mixed Alzheimer's disease vascular in lobar intracerebral haemorrhage.

Patients and methods

Inclusion and exclusion criteria

The Prognosis of Intracerebral Haemorrhage (PITCH) cohort is an observational study that recruited patients from November 2004 to April 2009. We prospectively collected data on all adults admitted as emergencies in the Lille University Hospital for acute stroke, who had parenchymal haemorrhage on the computed tomographic scan performed at admission. Pure intraventricular haemorrhages were not included. We did not include patients who had, on admission, definite evidence as cause of intracerebral haemorrhage for intracranial vascular malformation, head trauma, tumour or haemorrhagic transformation within an infarct. We did not recruit patients referred from other hospitals; the 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 patients with intracerebral haemorrhage recruited in the population-based Dijon stroke registry (Cordonnier *et al.*, 2009). Therefore, the PITCH cohort has an excellent external validity, in line with recommendations for observational studies (von Elm *et al.*, 2007).

Demographic characteristics and medical history

We prospectively collected the following demographic characteristics: age, gender and educational level (≤ 8 years of education versus >8 years). We determined vascular risk factors according to the medical history provided by the patient, family or general practitioner as previously described (Cordonnier *et al.*, 2009). We recorded history of previous stroke or transient ischaemic attack, ischaemic heart disease, atrial fibrillation, dementia and family history of stroke or dementia. We evaluated the pre-existing level of dependency with the modified Rankin Scale (van Swieten *et al.*, 1988), patients with modified Rankin Scale scores of ≥ 3 being considered dependent.

Evaluation of pre-existing cognitive decline and dementia

The systematic assessment of pre-existing dementia was conducted within 48 h of stroke onset by a French translation of the short version of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) (Jorm, 1994). This questionnaire consists of 16 questions regarding the changes experienced by the patient over the last 10 years in aspects of daily behaviour requiring memory and other intellectual abilities. A close relative needs to be interviewed and therefore the IQCODE does not require the participation of the patient when neuropsychological functions and consciousness may be influenced by intracerebral haemorrhage. We classified as having cognitive decline patients with either: (i) cognitive impairment with no dementia, with IQCODE scores between 53 and 63; (ii) pre-existing dementia, with IQCODE scores of >64 (Jorm, 1994).

Clinical assessment

We evaluated the severity of the neurological deficit by the National Institute of Heath Stroke Scale at admission (National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group, 1995) and the intrahospital mortality.

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. Images were reviewed in the Digital Imaging and Communications in Medicine (DICOM) format by a study investigator who was blinded to the clinical data and not involved in the management of the patients. The location of the intracerebral haemorrhage was considered: (i) lobar (frontal, temporal, parietal and occipital) when the origin of the haemorrhage appeared to be in the cerebral hemispheres 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 haemorrhage when the origin could not be reliably identified. We also collected data on the presence of old territorial vascular lesions, old lacunes, cortical atrophy (Leys *et al.*, 1989) and leucoaraiosis (Blennow *et al.*, 1991). We calculated the volume of the intracerebral haemorrhage according to the $A \times B \times C/2$ method (Kothari *et al.*, 1996).

Neuropathology

Patients who died were autopsied when possible. Collected brains were freshly split in half. The hemisphere without the intracerebral haemorrhage was deep frozen ($-80°C$) for further biochemical and molecular analyses. The hemisphere with the intracerebral haemorrhage, cerebellum and brainstem were fixed in buffered formalin solution for 6 weeks and subsequently sampled for histopathological analyses. For all brains collected, immunohistochemistry of τ-protein, β-amyloid and α-synuclein was performed according to BrainNet Europe Consortium recommendations (Alafuzoff et al., 2008). Neurofibrillary pathology was quantified according to Braak stages (Braak and Braak, 1996). Amyloid deposition was quantified according to Thal and Braak stages (Thal et al., 2002). The neuropathological diagnosis of Alzheimer's disease was based on the National Institute on Aging and Reagan Institute (NIA-RI) working group recommendations (1997). The diagnosis of definite cerebral amyloid angiopathy was based on the Boston criteria (Knudsen et al., 2001). Ischaemic and haemorrhagic lesions, as well as white matter changes and vessel wall pathology, were assessed as previously reported (Bruandet et al., 2009).

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.

Statistical analyses

To determine whether patients with a reliable informant, compulsory for the IQCODE evaluation, were representative of the whole PITCH cohort, we compared the main baseline characteristics and intrahospital mortality between patients with and without IQCODE, using the chi-square test for categorical variables and the Mann–Whitney U-test for continuous variables. We described the prevalence of cognitive impairment with no dementia and pre-existing dementia, with 95% confidence intervals (CI) and compared factors associated with the three groups of patients (no dementia, cognitive impairment with no dementia and pre-existing dementia) with bivariate analyses (chi-square and Kruskal–Wallis tests where appropriate). We then performed an ascending stepwise logistic regression analysis with IQCODE score (quoted 1 when $\geq$64 and 0 when <64) as the dependent variable. Variables were selected from the bivariate analysis (no dementia versus pre-existing dementia) with a 0.2 level as a screening criterion for selection of candidate variable. We included in the logistic regression model the following variables: age, gender, level of education, previous stroke or transient ischaemic attack, ischaemic heart disease, cortical atrophy score, leucoaraiosis score, old territorial vascular lesions, old lacunes and location of the intracerebral haemorrhage (lobar versus non-lobar). We repeated the analysis for patients having had their first stroke: the variables selected for the multivariate model were age, gender, level of education, cortical atrophy score, leucoaraiosis score, old territorial vascular lesions, old lacunes and location of the intracerebral haemorrhage (lobar versus non-lobar). Because of the influence of location, we repeated the analyses (bivariate—data not shown—then multivariate) separately in two groups of patients: lobar intracerebral haemorrhage only and deep intracerebral haemorrhage only. Multivariate analyses included the following variables: (i) for lobar intracerebral haemorrhage: age, gender, level of education, previous history of stroke or transient ischaemic attack, ischaemic heart disease, familial history of dementia, old territorial vascular lesions, cortical atrophy score and leucoaraiosis score and (ii) for deep intracerebral haemorrhage: level of education, previous history of stroke or transient ischaemic attack, old territorial vascular lesions, cortical atrophy score and leucoaraiosis score. We performed the statistical analysis with the Statistical Package for the Social Sciences (SPSS) v15.0 package for Windows and CI analysis software (Bryant, 2000).

Results

Baseline characteristics and outcome of patients without a reliable informant

Among the 562 patients (median age 72 years, interquartile range 58–79), 145 (26%, 95% CI 22–30%) had no informant; they were more likely to have atrial fibrillation and ischaemic heart disease and to be alcoholic and dependent before intracerebral haemorrhage, to have more severe strokes with higher National Institutes of Heath Stroke Scale (NIHSS) scores at admission, higher intracerebral haemorrhage volumes and more frequently multiple intracerebral haemorrhage, resulting in higher intrahospital death rates. Among those 145 patients, only one patient had been diagnosed as demented without specific treatment or referral to a memory clinic. Data are provided in Table 1.

Study population

The study population consisted of 417 patients (211 males; 51%, 95% CI 46–55%) with a median age of 72 years (interquartile range 58–79).

Prevalence of cognitive decline

One hundred and twenty-three (29%; 95% CI 25–34%) patients had pre-existing cognitive decline.

Fifty-eight (14%; 95% CI 11–18%) patients had cognitive impairment with no dementia. None had been identified as demented before intracerebral haemorrhage. Only one patient had been diagnosed with cognitive decline without specific treatment or referral to a memory clinic. The prevalence of cognitive impairment with no dementia was 19% (95% CI 13–26%) in the lobar intracerebral haemorrhage group, 13% (95% CI 9–18%) in the deep intracerebral haemorrhage group and 9% (95% CI 4–22%) in the posterior fossa intracerebral haemorrhage group.

Sixty-five (16%; 95% CI 12–19%) patients met the criteria for pre-existing dementia. The results of the bivariate analyses are detailed in Table 2. Thirty-seven (57%) of these had previously been diagnosed as having dementia: 15 were considered as having Alzheimer's disease (11 had lobar intracerebral haemorrhage) and 10 were treated with acetylcholinesterase inhibitors; five were considered as having vascular dementia (two had lobar intracerebral haemorrhage) and none of them were treated with acetylcholinesterase inhibitors; three were considered as having mixed Alzheimer-vascular dementia (none had lobar intracerebral haemorrhage), with one being treated with acetylcholinesterase inhibitors. In 14 patients, the presumed cause was undetermined (eight had lobar intracerebral haemorrhage), with one being

Table 1 Comparison between patients with and without an informant

	No reliable informant (n = 145) (%)	Informant available (n = 417) (%)	P
Demographics			
Age[a]	72 (60–80)	72 (58–79)	0.349
Female gender	63 (43)	206 (48)	0.216
≤8 years of education[b]	23 (70)	230 (62)	0.361
Vascular risk factors			
Arterial hypertension[c]	96 (68)	265 (63)	0.330
Diabetes[c]	27 (19)	58 (14)	0.134
Hypercholesterolemia[c]	47 (33)	120 (29)	0.307
Smoking[d]	28 (24)	76 (18)	0.186
Alcoholism[e]	40 (32)	97 (23)	**0.039**
Medical history			
Atrial fibrillation[c]	31 (22)	50 (12)	**0.004**
Coronary heart disease[c]	28 (20)	54 (13)	**0.014**
History of stroke of TIA[c]	29 (21)	82 (20)	0.816
Functional status			
Prestroke modified Rankin >2[f]	49 (48)	127 (31)	**0.001**
Radiological data			
ICH location[g]			0.449
Posterior fossa	20 (15)	43 (11)	
Deep	62 (47)	207 (52)	
Lobar	45 (34)	138 (35)	
Undetermined origin	5 (4)	10 (2)	
Multiple ICH	13 (9)	19 (5)	**0.048**
Volume (ml)[a]	47 (12–104)	16 (5–42)	**<0.0001**
≥1 old territorial vascular lesions	17 (14)	70 (17)	0.373
≥1 lacunes	39 (32)	141 (35)	0.515
Leucoaraiosis score[a]	1.5 (1–2.5)	1.5 (0–2.5)	0.146
Cortical atrophy score[a]	2 (1–2)	2 (1–2)	0.102
Severity of stroke			
NIHSS score at admission[a]	28 (16–38)	14 (6–23)	**<0.0001**
Outcome			
In-hospital mortality	115 (79)	131 (31)	**<0.0001**
Delay of death (days)[a]	1 (1–2)	4 (1–9)	

Results of the bivariate analysis. Data are numbers, using chi-square test unless specified.
P values are in bold when significant.
a Median (interquartile range), using Mann–Whitney U-test.
b Missing data for 156 patients.
c Missing data for 4 patients.
d Missing data for 27 patients.
e Missing data for 22 patients.
f Missing data for 44 patients.
g Results provided are those of single bleeds only.
ICH = intracerebral haemorrhage; TIA = transient ischaemic attack.

treated with acetylcholinesterase inhibitors. The prevalence of pre-existing dementia was 23% (95% CI 17–31%) in the lobar intracerebral haemorrhage group, 12% (95% CI 8–17%) in the deep intracerebral haemorrhage group and 9% (95% CI 4–22%) in the posterior fossa intracerebral haemorrhage group. In each location, prevalence of pre-existing dementia varied among first and recurrent strokes (ischaemia or intracerebral haemorrhage) (Fig. 1).

Ongoing therapies before intracerebral haemorrhage

Ongoing therapies before intracerebral haemorrhage are detailed in Table 3. The proportion of patients treated with statins, anti-hypertensive agents, anti-diabetic agents or anti-coagulants did not differ among patients without cognitive decline, with cognitive impairment with no dementia or with pre-existing dementia. Patients without cognitive decline were less frequently treated with anti-platelet agents (P = 0.001).

Factors associated with pre-existing dementia in the overall study population

Factors independently associated with pre-existing dementia were increasing age (odds ratio: 1.05/1 year; 95% CI 1.01–1.10), having <8 years of education (odds ratio: 5.25; 95% CI 1.90–14.52), old territorial vascular lesions (odds ratio: 3.35; 95% CI 1.40–8.02), lobar location of intracerebral haemorrhage (odds ratio: 3.39; 95% CI 1.52–7.57), increasing leucoaraiosis score (odds ratio: 1.91 per one step; 95% CI 1.19–3.08) and increasing cortical atrophy score (odds ratio: 1.90 per one step, 95% CI 1.04–3.47).

Factors associated with pre-existing dementia among patients with first stroke

Among patients with first stroke (n = 352), 12% were demented before onset of intracerebral haemorrhage. Factors independently associated with pre-existing dementia were having <8 years of education (odds ratio: 9.43; 95% CI 2.34–37.94), lobar location of intracerebral haemorrhage (odds ratio: 5.62; 95% CI 2.00–15.81), increasing leucoaraiosis score (odds ratio: 3.33 per one step; 95% CI 1.76–6.31) and increasing cortical atrophy score (odds ratio: 2.86 per one step; 95% CI 1.34–6.11). Compared with the overall population, two variables were no longer associated with pre-existing dementia: increasing age and the presence of old territorial vascular lesions. Among patients with recurrent strokes (n = 65), 37% were demented before intracerebral haemorrhage onset. Because of the small number of patients with a recurrent stroke, multivariate analyses were not performed (Fig. 1).

Factors associated with pre-existing dementia among patients with lobar or deep intracerebral haemorrhage

Factors independently associated with pre-existing dementia among patients with lobar intracerebral haemorrhage (n = 138) were increasing age (odds ratio: 1.09/1 year; 95% CI 1.02–1.15), having <8 years of education (odds ratio: 8.37; 95% CI 1.91–36.65) and increasing cortical atrophy score (odds ratio: 3.34 per one step; 95% CI 1.40–7.96). Among patients with deep intracerebral haemorrhage (n = 207), factors independently associated with pre-existing dementia were the presence of old territorial lesions (odds ratio: 3.98; 95% CI 1.06–14.92) and increasing leucoaraiosis score (odds ratio: 3.87 per one step; 95% CI 1.66–9.02).

Table 2 Characteristics of patients without cognitive decline, with cognitive impairment with no dementia and with pre-existing dementia

	No cognitive decline (n = 294) (%)	Cognitive impairment with no dementia (n = 58) (%)	Pre-existing dementia (n = 65) (%)	P
Demographics				
Age[a]	66 (54–77)	76 (71–82)	78 (75–84)	<0.0001
Female gender	137 (47)	30 (52)	39 (60)	0.157
≤8 years of education[b]	156 (59)	31 (55)	43 (84)	0.001
Vascular risk factors				
Arterial hypertension	181 (62)	44 (76)	40 (62)	0.163
Diabetes	38 (13)	9 (16)	11 (17)	0.637
Hypercholesterolemia	80 (27)	20 (35)	20 (31)	0.523
Smoking	56 (19)	6 (10)	14 (22)	0.195
Alcoholism	71 (24)	13 (22)	13 (20)	0.782
Medical history				
Atrial fibrillation	30 (10)	11 (19)	9 (14)	0.163
Ischaemic heart disease	28 (9)	11 (19)	15 (23)	0.004
History of stroke or TIA	37 (13)	20 (35)	25 (39)	<0.0001
Familial history of stroke[c]	80 (28)	18 (32)	15 (29)	0.894
Familial history of dementia[d]	20 (7)	9 (16)	6 (13)	0.098
Functional status				
Prestroke modified Rankin > 2	46 (16)	24 (41)	57 (88)	<0.0001
Radiological data				
ICH location[e]				0.010
Posterior fossa	35 (12)	3 (5)	5 (8)	
Deep	157 (56)	26 (46)	24 (39)	
Lobar	80 (29)	26 (46)	32 (52)	
Undetermined origin	8 (3)	1 (2)	1 (2)	
Multiple ICH	14 (5)	2 (3)	3 (5)	0.898
Volume (ml)[a]	14 (5–34)	15 (2–54)	27 (6–62)	0.125
≥1 old territorial vascular lesions	33 (12)	14 (26)	23 (38)	<0.0001
≥1 lacunes	94 (33)	26 (46)	22 (37)	0.118
Leucoaraiosis score[a]	1 (0–2)	2 (1–3)	2.5 (1–3)	<0.0001
Cortical atrophy score[a]	1 (1–2)	2 (2–3)	2 (2–3)	<0.0001
Severity of stroke				
NIHSS score at admission[a]	13 (6–22)	16 (4–23)	17 (9–26)	0.060
Outcome				
In-hospital mortality	82 (28)	24 (41)	25 (39)	0.056

Results of the bivariate analyses concerned the comparison of the three groups of patients. Data are numbers. Statistics used chi-square test unless specified.
a Median (interquartile range, Kruskal–Wallis test).
b Missing data for 44 patients.
c Missing data for 27 patients.
d Missing data for 38 patients.
e Results provided are those of single bleeds only.
ICH = intracerebral haemorrhage; TIA = transient ischaemic attack.

The prevalence of old vascular lesions (territorial lesions and/or lacunes) was higher in deep intracerebral haemorrhage (52%) than in lobar intracerebral haemorrhage (39%) (P = 0.025) (Supplementary Table 1).

Presumed causes of pre-existing dementia

Among the 25 patients with pre-existing dementia who died within the first 2 weeks after admission, five (20%) came to

autopsy. Post-mortem delay ranged between 3 and 18 h after death and between 2 and 12 days after onset of intracerebral haemorrhage. One of the patients had a deep intracerebral haemorrhage (Fig. 2): this 76-year-old male had suffered from a previous deep intracerebral haemorrhage 21 years before and had not been identified as demented before intracerebral haemorrhage despite an IQCODE score of 65. Brain examination showed features of severe small-vessel disease (lipohyalinosis in deep perforating arteries) and severe subacute and chronic ischaemic changes among cortical areas, basal ganglia and white matter. Some atherosclerotic lesions were observed in the arteries of the
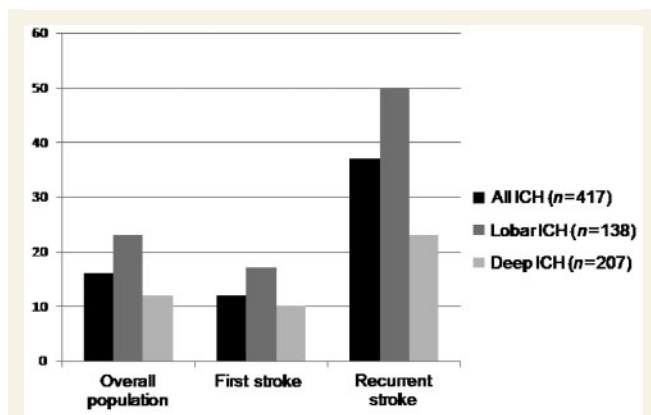
Figure 1 Prevalence of pre-existing dementia among first and recurrent stroke patients, according to the location of the intracerebral haemorrhage (ICH).

Table 3 Ongoing therapies before intracerebral haemorrhage of patients without cognitive decline, with cognitive impairment with no dementia and with pre-existing dementia

	No cognitive decline (n = 294) (%)	Cognitive impairment no dementia (n = 58) (%)	Pre-existing dementia (n = 65) (%)	P
Anti-platelet drugs	70 (24)	24 (41)	28 (43)	0.001
Oral anticoagulants	37 (13)	9 (16)	9 (14)	0.822
Statins	50 (17)	13 (22)	16 (25)	0.282
Anti-diabetic drugs	29 (10)	8 (14)	6 (9)	0.636
Anti-hypertensive drugs	161 (55)	39 (67)	39 (60)	0.191

Results of the bivariate analyses concerned the comparison of the three groups of patients.
Data are numbers. Statistics used chi-square test.

circle of Willis. There was no evidence of definite Alzheimer's disease or cerebral amyloid angiopathy, enabling a diagnosis of pure vascular dementia. Four patients had suffered from lobar intracerebral haemorrhage: (i) a 78-year-old female treated with memantine and donepezil for Alzheimer's disease who had an IQCODE score of 80; (ii) an 84-year-old female treated with memantine and donepezil for Alzheimer's disease who had an IQCODE score of 80; (iii) a 76-year-old female who had not been diagnosed as demented despite an IQCODE score of 72 and (iv) an 89-year-old female treated with memantine and donepezil for Alzheimer's disease who had an IQCODE score of 80. A sixth post-mortem case was obtained, a 68-year-old female not considered as cognitively impaired before intracerebral haemorrhage despite an IQCODE score of 53. Therefore she was considered as having cognitive impairment with no dementia. She suffered from a lobar intracerebral haemorrhage and died 7 months later (Fig. 3). At autopsy, the five patients with lobar intracerebral haemorrhage had definite cerebral amyloid angiopathy associated with Alzheimer's disease pathology: stage V of Braak for the first four and stage VI


Figure 2 CT scan at admission of a 76-year-old male, showing a left deep intracerebral haemorrhage (arrow). He had suffered from a previous right deep intracerebral haemorrhage 21 years before (arrow) and had not been identified as demented before intracerebral haemorrhage despite an IQCODE score of 65. Brain examination showed features of severe small-vessel disease. There was no evidence of Alzheimer's disease pathology, enabling a diagnosis of pure vascular dementia.

associated with widespread microscopic cortical and subcortical chronic infarcts and remote haemorrhages for the last case (Fig. 3). None of these autopsied cases had neuropathological features of Lewy body disease. Among patients without pre-existing cognitive decline, one came to autopsy: an 88-year-old female who died 4 days after onset of deep intracerebral haemorrhage. She had no cognitive decline (IQCODE score 48). Post-mortem study showed features of moderate small-vessel disease, age-related neurofibrillary changes (Braak stage III), rare and diffuse amyloid deposits, but no evidence of cerebral amyloid angiopathy.

Discussion

Our study found a prevalence of pre-existing dementia of 16% in a large prospective intracerebral haemorrhage cohort with a strong influence of recurrent stroke, since only 12% of patients who suffered a first stroke were demented before intracerebral haemorrhage versus 37% of patients who suffered from a recurrent stroke. Lobar location of the intracerebral haemorrhage was strongly associated with pre-existing dementia. In lobar intracerebral haemorrhage, associated factors (increasing age, low educational level and severity of atrophy) suggested a neurodegenerative process. This was confirmed by autopsy in five cases that all had Alzheimer's disease and cerebral amyloid angiopathy. In deep intracerebral haemorrhage, associated factors
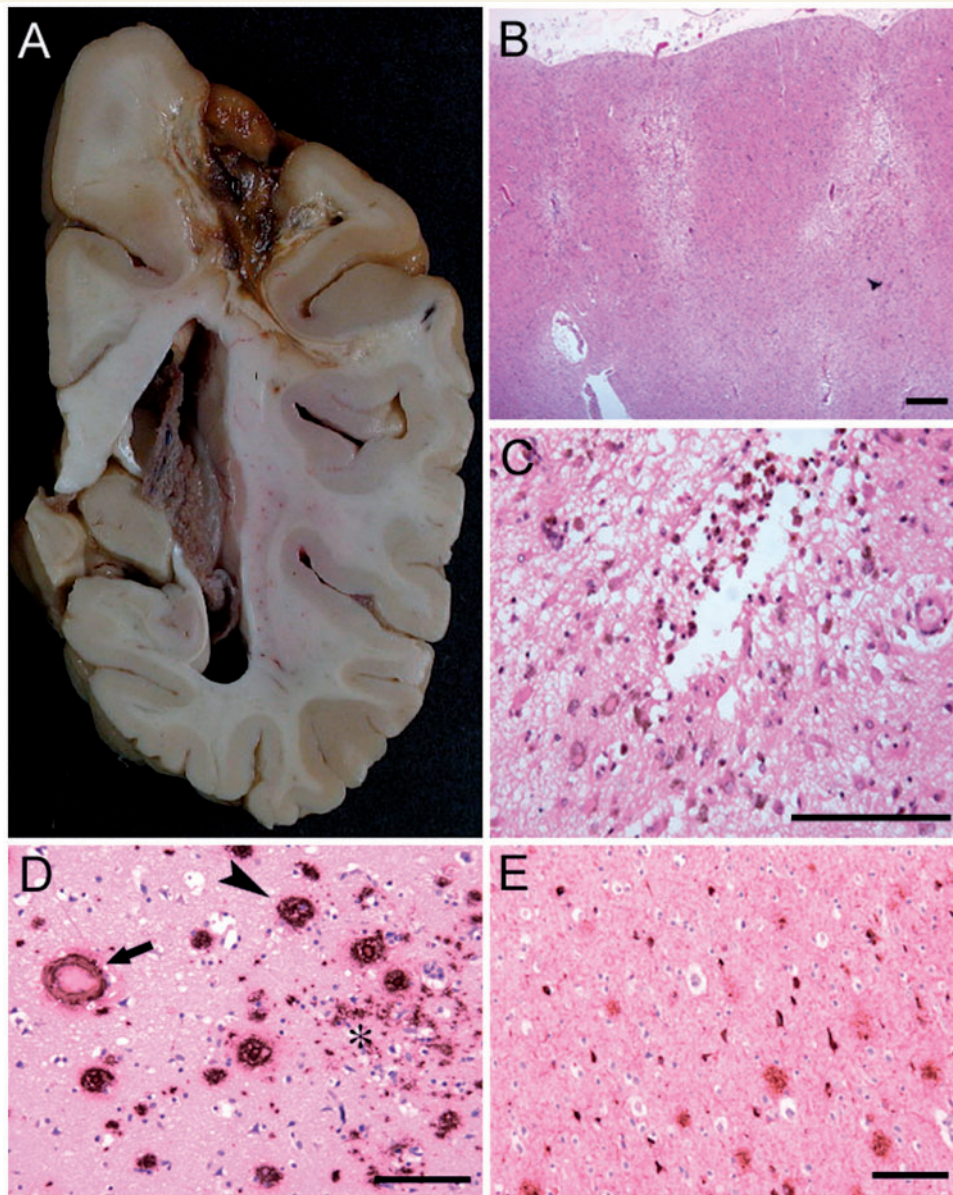
Figure 3 Neuropathological findings in a 68-year-old female who died 7 months after onset of lobar intracerebral haemorrhage. The final diagnosis was definite cerebral amyloid angiopathy with severe Alzheimer's disease lesions (Braak stage for neurofibrillary lesions VI). (**A**) Lobar haemorrhagic scar located near the right central sulcus. (**B**) Multiple cortical microinfarcts (right anterior cingulated gyrus, haematoxylin and eosin stain). (**C**) Higher power view of a remote microhaemorrhage with peripheral gliosis and microglial haemosiderin resorption (right temporal cortex, haematoxylin and eosin stain). (**D**) Various beta amyloid deposits with focal (arrowhead), diffuse (asterisk) and vascular (arrow) staining (right occipital cortex, Aβ immunohistochemistry). (**E**) Abundant neurofibrillary tangles and neuritic plaques (right frontal cortex, τ-immunohistochemistry). Scale bar for all images 100 µm.

(old territorial vascular lesions and severity of leucoaraiosis) suggested a vascular process that was confirmed by one autopsy case showing features of severe small-vessel disease without Alzheimer's disease lesions.

This is the first prospective study in a large cohort of consecutive patients with intracerebral haemorrhage that focused on pre-existing dementia using a systematic, standardized cognitive evaluation and included post-mortem examinations. The PITCH cohort combines the advantage of hospital-based recruitment (enabling a large sample size with detailed and standardized data collection with few missing data, including post-mortem data) with an excellent external validity close to a population-based recruitment (Cordonnier et al., 2009). We designed a careful evaluation with a standardized and validated questionnaire, the IQCODE (Jorm, 1994; Pendlebury and Rothwell, 2009). To be specific in our criteria for dementia and to avoid bias, we excluded patients without a reliable informant. To perform a cognitive assessment with the IQCODE, the quality of the informant is

very important. The informant needed to know the patient for at least 10 years and also had to meet the patient frequently. We chose to be very strict on the quality of the informant for the cognitive assessment in order to be as specific as possible for the diagnosis of dementia. Moreover, in a few cases, family members were not French speakers and we were not able to perform a detailed questionnaire on cognition. This is why sometimes we were able to assess independence before intracerebral haemorrhage (using the modified Rankin scale) with a person who did not qualify as a 'reliable' informant for the IQCODE. In some cases, patients themselves were able to talk and to describe their level of dependency but were isolated and we were not able to meet with a reliable informant within the first 48 h of stroke. We had to exclude 145 (26%) patients without an informant, this proportion being similar to that reported in previous studies (Hénon *et al.*, 1997). Patients who were excluded because of a lack of informant had significantly higher premorbid modified Rankin scores and more severe stroke. These factors were significantly associated with pre-intracerebral haemorrhage dementia (in bivariate analyses). It is thus possible that we slightly underestimated the prevalence of pre-intracerebral haemorrhage dementia in the overall cohort. Our finding of 12% of pre-existing dementia among patients with first strokes is, however, in line with the pooled results from a recent systematic review (Pendlebury and Rothwell, 2009). This finding is striking, since in the published literature to date, most studies were conducted mainly in ischaemic stroke cohorts.

Associated factors with pre-existing dementia previously reported in the literature were increasing age, female gender, low educational level, severity of cerebral or temporal lobe atrophy, previous stroke or transient ischaemic attack, severity of leucoaraiosis, multiple infarcts, diabetes, atrial fibrillation and arterial hypertension (Pendlebury and Rothwell, 2009). Because of the heterogeneity of the methods previously used, it was difficult to disentangle the influence of recurrent strokes or of the nature of the stroke itself. Our focus on intracerebral haemorrhage only highlighted the fact that some variables such as atrial fibrillation or diabetes might have been confounded by the nature of the stroke. Moreover, our subgroup analysis focusing on first strokes suggested that increasing age, previous stroke or transient ischaemic attack, or multiple infarcts might have been confounded by the inclusion of recurrent strokes.

More than half of the patients with dementia had previously been diagnosed, which is huge progress compared with only 3% of patients identified as demented before stroke onset in our institution 15 years ago (Hénon *et al.*, 1997). This significant increase highlights the improvement of medical awareness of dementia, although 43% of patients with dementia were still undiagnosed. Regarding cognitive impairment with no dementia, our results remain worrisome; though frequent (one patient with intracerebral haemorrhage out of seven had cognitive impairment with no dementia), only a few patients had been identified with cognitive decline. These patients are at high risk of developing post-stroke dementia (Hénon *et al.*, 2001) and of being institutionalized (Pasquini *et al.*, 2007). Therefore, clinicians should pay particular attention to cognitive status in patients with intracerebral haemorrhage.

As shown in a systematic review, variations in reported prevalence of pre-stroke dementia are mainly due to methodological heterogeneity (Pendlebury and Rothwell, 2009). In a study on functional outcome in a cohort of 629 patients with intracerebral haemorrhage, only 15% (95% CI 13–18%) of patients had pre-intracerebral haemorrhage cognitive impairment (Rost *et al.*, 2008). The discrepancy with our results may be explained by methodological heterogeneity, which included the use of a composite criterion in a study that did not focus on cognition. Unfortunately, no data were available on dementia. In a study focusing on 182 patients with lobar intracerebral haemorrhage aged >55 years, the prevalence of pre-intracerebral haemorrhage cognitive impairment was 23% (95% CI 18–30%), which is slightly lower than in our population, although the mean age of 80 years in patients with cognitive impairment was higher than in our cohort (Smith *et al.*, 2004). In this selected population with a high education level, the authors did not use a standardized questionnaire, and data on dementia were not available. Moreover, no post-mortem data were reported regarding the cause of cognitive decline.

No neuropathological data are available in the literature to determine the presumed cause of pre-existing cognitive decline in intracerebral haemorrhage. Our study is the first to provide insight into the cause of pre-existing dementia. Although only six patients with pre-existing dementia came to autopsy, post-mortem examinations strongly supported the results of clinical findings that suggested a vascular process in deep intracerebral haemorrhage and Alzheimer's disease pathology with cerebral amyloid angiopathy in lobar intracerebral haemorrhage. We suggest that the vasculopathy resulting in an intracerebral haemorrhage is also responsible for the cognitive disorders. Directly acting on the vessel disease may therefore result in the prevention of both intracerebral haemorrhage and dementia. These results should be confirmed with larger sample sizes.

The major limitation of our study is the use of computed tomography scans precluding a precise anatomical description of atrophy. We hypothesized that cortical atrophy was due to neurodegenerative damage. However, we cannot exclude that it may also reflect white-matter atrophy due to vascular damage. Further imaging studies with MRI will be necessary. Other MRI biomarkers such as brain microbleeds should also be prospectively studied and validated as diagnostic and prognostic markers (Greenberg *et al.*, 2009), not only for the cause of the cognitive decline but also for the cause of the intracerebral haemorrhage. Considering 'spontaneous' intracerebral haemorrhage as a single entity is misleading. The underlying disease of the brain vessel is important not only for understanding (and eventually treating) the cause of the bleeding but also for understanding the nature of the associated cognitive disorders.

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Supplementary material

Supplementary material is available at *Brain* online.

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