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REVIEW

Biological and imaging predictors of cognitive impairment after stroke: a systematic review

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Abstract

Background Cognitive impairment is frequent after stroke, and several studies have suggested that biological and imaging characteristics present before stroke are associated with the development of post-stroke cognitive impairment.

Objective The aim of our study was to systematically review biological and imaging predictors of cognitive impairment after stroke.

Method Studies were identified from bibliographic databases and reference lists, and were included if conducted in patients with acute stroke, with at least 30 patients, and a follow-up of at least 3 months. We included articles on potential biomarkers of cognitive impairment that pre-existed to stroke.

Results We identified 22,169 articles, including 20,349 with abstract. After analysis, 66 studies conducted in 42 cohorts met selection criteria. They included 30–9522 patients [median 170; interquartile range (IQR) 104–251] with a median follow-up of 12 months (IQR 3–36). All studies met quality criteria for description of the study population and standardization of biomarkers. Twenty-nine studies met all quality criteria. There was no convincing evidence that any biological marker may predict cognitive impairment. The most consistent predictors of cognitive impairment after stroke were global atrophy and medial temporal lobe atrophy.

Conclusion Pre-existing cerebral atrophy is the most consistent predictor of cognitive impairment that can be identified in patients with an acute stroke.

Keyword Brain infarction · Intracerebral haemorrhage · Cognitive disorders · Dementia · Vascular dementia

Introduction

Stroke is a major public health issue worldwide because of the high risk of death and disability leading to a significant burden for the patients, their families and the society [1]. Cognitive impairment accounts for an important part of disability after stroke: previous studies on the prevalence of dementia 1 year after stroke showed that 7.4–41.3% of patients have criteria for dementia after stroke, this huge variability being explained by methodological heterogeneities [2].

Patients at highest risk for cognitive impairment should be identified at the acute stage of stroke, because they are likely to benefit from more intensive follow-up focused on cognition. Several stroke characteristics are thought to be associated with an increased risk of dementia, but there are inconsistencies in the literature. Reported risk factors are heterogeneous, including haemorrhagic stroke [3], lobar location of a parenchymal haemorrhage [4], presence of aphasia, multiple strokes, stroke volume, occurrence of complications [2], demographic characteristics (e.g., female sex, non-white ethnicity, and low education), or presence of vascular risk factors [2]. It is therefore crucial to identify biomarkers of future dementia or cognitive decline in the acute phase of stroke.

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We aimed to carry out a systematic review of studies on biological and imaging predictors of cognitive impairment after stroke.

Methodology

Literature search strategy

On 31st July 2018, we searched Ovid Medline from 1966, Embase from 1980, and Cochrane library using the following key words: "stroke [or] cerebral infarct [or] brain infarct [or] cerebral haemorrhage [or] cerebral ischaemia [or] cerebral haematoma [or] brain haemorrhage" [and] "dementia [or] cognitive decline [or] cognitive impairment [or] cognition" (title/abstract/Mesh terms). We restricted this review to articles on humans and with abstract, irrespective of the language. The electronic search was supplemented by authors' personal files.

Selection of articles

Articles relevant for this study were selected per the following criteria:

- The inclusion criterion in the study is the clinical manifestation of stroke. The presence of patients with transient ischemic attacks (TIA) in the study was not an exclusion criterion. Articles on clinically silent strokes, subarachnoid haemorrhages, and traumatic or malformative intracerebral haemorrhages, and cerebro-vascular disorders without strokes (dissections and venous thrombosis without stroke) were excluded.
- Enrolled patients were 18 years old or more.
- At least 80% of patients underwent at least 1 CT or MRI scan. The percentage had to be clearly stated in the article or in a previous article from the same group on the same cohort.
- The study included at least 30 patients.
- Patients underwent at least one cognitive evaluation, 3 months or more after stroke.
- Potential biomarkers of cognitive impairment pre-existing to stroke.

Three authors (BC, FC, DL) performed the literature search and screened titles and abstracts for potentially suitable studies. A first step exclusion was based on abstracts. Check for eligible criteria was thereafter carried out on article content. We resolved disagreements between reviewers by discussion and consensus. The last step consisted in exclusion of duplicates. In case of duplicates on the same cohort, the most recent article was selected for analysis.

Data extraction

Three reviewers performed data extraction. We critically evaluated studies according to a customized checklist of ideal characteristics for a study of predictors of post-stroke cognitive impairment (Table 1), according to guidelines by the Cochrane collaboration, QUality Assessment of Diagnostic Accuracy Studies (QUADAS) [5] and Standards for the Reporting of Diagnostic Accuracy (STARD) [6]. We excluded studies investigating biological or radiological biomarkers included in a composite score (when the score included other variables rather than radiological or biological) to predict post-stroke cognitive impairment.

Critical quality evaluation

For critical quality evaluation, we extracted attributes of the study design, details of demographics, clinical and cognitive assessments, biological and imaging markers.

Table 1 Ideal design of studies of predictors of post-stroke cognitive impairment

Inclusion criterion in the study is a stroke or a TIA*
Recruitment of consecutive patients
Inclusion of at least 30 patients at baseline*
Inclusion of at least 80% of patients with CT or MRI scan or autopsy after stroke*
Selection criteria of study population clearly described
Pre-stroke cognition analyzed by IQCODE [42] or equivalent standardized test
Statement on inclusion or not of patients with pre-existing cognitive impairment or dementia
Includes at least one cognitive follow-up 3 months or more after stroke*
Post-stroke global cognitive state diagnosed by standardized criteria
Adjustment on known predictors of post-stroke cognitive impairment
Standardized evaluation of biomarkers
Methodology detailed enough to allow replication

TIA transient ischemic attack, *CT* computed tomographic, *MRI* magnetic resonance imaging, *IQCODE* Informant Questionnaire on Cognitive Decline in the Elderly

*Criteria requested for eligibility in the study

Analysis of articles

We analyzed potential biological or imaging markers that were studied in at least two independent articles. Markers studied in one single article were just cited.

Results

The electronic search of Medline and Embase identified 22,169 articles, including 20,349 with abstract. After exclusion of non-eligible articles based on the abstract content, and analysis of the articles when appropriate, 66 met selection criteria for the study. They reported research conducted in 42 independent cohorts, including 30–9,522 patients [median 170; interquartile range (IQR) 104–251] with a median follow-up of 12 months (IQR 3–36).

Quality assessment of the selected articles

Details on quality criteria of the 66 selected articles are provided in Table 2. All studies met quality criteria for a clear description of the selection criteria of the study population and for standardization of the biomarkers included in the analysis. Among the 66 selected studies, 29 met all the quality criteria [4, 7–34]. 7 studies did not recruit consecutive patients [35–41], 17 did not use the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) [42] or any other standardized evaluation of the pre-existing cognitive status [39, 40, 43–56], 6 did not state whether patients with pre-existing cognitive impairment or dementia were excluded or not [37, 39, 40, 46, 50, 56], 10 did not use standardized criteria for diagnosis of post-stroke cognitive impairment or dementia [40, 46, 51, 57–63], and 12 did not adjust for known predictors of post-stroke cognitive impairment [35, 46, 48, 61, 64–71].

Methodological assessment of the selected articles

The methodology of the 66 selected articles is detailed in Tables 1s and 2s (online supplementary material).

Biomarkers evaluated in the selected articles

Biomarkers evaluated in the selected articles are detailed in Tables 3 and 3s (supplementary material).

- *Imaging markers* White matter changes (WMC) were evaluated in 35 articles, and they were found associated with an increased risk of cognitive impairment or dementia in 12 studies [4, 9, 19, 20, 23, 34, 41, 45, 49–51, 61]. In two other studies, WMC resulted as independent predictors only if pre-existent cognitive impairment was not taken into account [11, 44]. In 11 studies, WMC were associated with cognitive impairment only in univariate analyses [12, 25, 26, 48, 52, 53, 58, 59, 66, 67, 71]. In eight studies, WMC were not associated with post-stroke cognitive impairment [14–16, 18, 21, 35, 38, 64]. The terms "global" and "cortical" atrophy were often used to describe the same findings. Therefore, we included "cortical atrophy" as part of the definition of global atrophy. Global cerebral atrophy, irrespective of the method of evaluation (subjective assessment, dilatation of sulci, ventricular enlargement, voxel based measure) was associated with an increased risk of post-stroke dementia or cognitive impairment in 12 articles [4, 15, 16, 19, 26, 28, 41, 52, 57, 59, 63, 64], but not in three [21, 35, 67]. In other six studies, the significant association found by univariate analysis disappeared after adjustment [9, 18, 20, 38, 49, 53], and in four studies global cerebral atrophy was not included in the multivariate model because of a co-linearity with other variables, especially age [7, 11, 12, 66]. In one study, the result was not clear enough to draw any conclusion [14]. Medial temporal lobe atrophy (MTLA) was found to be a predictor of post-stroke dementia or cognitive impairment in seven studies [9, 12, 19, 38, 49, 53, 66], but the association disappeared after adjustment in one study [12], and two of these studies did not perform any adjustment on possible confounders [19, 66]. Silent infarcts (SI) and lacunes were evaluated in 14 independent studies [4, 8, 11, 12, 15, 25, 35, 41, 48, 52–54, 58, 59]. In three articles, they were independent predictors for cognitive impairment or dementia [11, 25, 59], but not in five [4, 8, 35, 41, 58]. In three articles, the association was lost after adjustment [12, 52, 53] and in two articles there was no adjustment [15, 48]. In one article, lacunes were significantly associated with post-stroke cognitive impairment in a selected population of lacunar stroke with MRI markers of small vessel disease [54]. Brain microbleeds were associated with the occurrence of dementia or cognitive impairment after stroke in three studies [4, 26, 72], while this association disappeared after adjustment in one [26]. Enlarged perivascular spaces (EPVS) were evaluated in three articles [52–54]. In one article, only basal ganglia location of EPVS was independently associated with post-stroke cognitive decline [52]. In the second study, the association disappeared after adjustment [53], and there was no significant association in the last study [54]. Intima media thickness was found as associated with post-stroke cognitive impairment in two independent cohorts [43, 68].
- *Biological markers* Of ten studies evaluating the influence of Apolipoprotein Epsilon 4 (APO E4) genotype on the occurrence of post-stroke cognitive impairment [10, 13, 24, 36, 37, 46, 60, 65, 69, 70], a positive association

Table 2 Quality assessment of the 66 selected articles

	Recruitment of consecutive patients	Selection criteria of study population clearly described	Pre-stroke cognition analyzed by IQCODE or equivalent	Statement on inclusion or not of patients with pre-existing cognitive impairment	Post-stroke cognitive state diagnosed by standardized criteria	Adjustment on known predictors of post-stroke cognitive impairment	Standardized evaluation of biomarkers	Methodology detailed enough to allow replication
Tatemichi et al. 1990 [57]	■	■	■	■	□	■	■	□
Loeb et al. 1992 [64]	■	■	■	■	■	□	■	■
Schmidt et al. 1993 [7]	■	■	■	■	■	■	■	■
Bornstein et al. 1996 [8]	■	■	■	■	■	■	■	■
Kase et al. 1998 [35]	□	■	■	■	■	□	■	■
Pohjasvaara et al. 2000 [9]	■	■	■	■	■	■	■	■
Barba et al. 2000 [10]	■	■	■	■	■	■	■	■
Henon et al. 2001 [11]	■	■	■	■	■	■	■	■
Cordoliani et al. 2003 [12]	■	■	■	■	■	■	■	■
Arpa et al. 2003 [13]	■	■	■	■	■	■	■	■
Ballard et al. 2004 [65]	■	■	■	■	■	□	■	■
Rasquin et al. 2004 [14]	■	■	■	■	■	■	■	■
Mok et al. 2004 [58]	■	■	■	■	□	■	■	■
Ivan et al. 2004 [36]	□	■	■	■	■	■	■	■
Tang et al. 2004 [15]	■	■	■	■	■	■	■	■
Talelli et al. 2004 [43]	■	■	□	■	■	■	■	■
Altieri et al. 2004 [16]	■	■	■	■	■	■	■	■
Klimkowicz et al. 2005 [17]	■	■	■	■	■	■	■	■
del Ser et al. 2005 [66]	■	■	■	■	■	□	■	■
Mok et al. 2005 [59]	■	■	■	■	□	■	■	■
Appelros et al. 2005 [44]	■	■	□	■	■	■	■	■
Martin-Ruiz et al. 2006 [60]	■	■	■	■	□	■	■	■
Sachdev et al. 2006 [67]	■	■	■	■	■	□	■	■
Tang et al. 2006 [18]	■	■	■	■	■	■	■	■
Lee et al. 2007 [68]	■	■	■	■	■	□	■	■
Pohjasvaara et al. 2007 [19]	■	■	■	■	■	■	■	■

Table 2 (continued)

	Recruitment of consecutive patients	Selection criteria of study population clearly described	Pre-stroke cognition analyzed by IQCODE or equivalent	Statement on inclusion or not of patients with pre-existing cognitive impairment	Post-stroke cognitive state diagnosed by standardized criteria	Adjustment on known predictors of post-stroke cognitive impairment	Standardized evaluation of biomarkers	Methodology detailed enough to allow replication
Thein et al. 2007 [45]	■	■	□	■	■	■	■	■
Baum et al. 2007 [46]	■	■	□	□	□	□	■	■
Cordonnier et al. 2007 [20]	■	■	■	■	■	■	■	■
Stebbins et al. 2008 [21]	■	■	■	■	■	■	■	■
Tamam et al. 2008 [47]	■	■	□	■	■	■	■	■
Sachdev et al. 2009 [69]	■	■	■	■	■	□	■	■
Delgado et al. 2010 [61]	■	■	■	■	□	□	■	■
Chausson et al. 2010 [48]	■	■	□	■	■	□	■	■
Wagle et al. 2010 [37]	□	■	■	□	■	■	■	■
Williamson et al. 2010 [22]	■	■	■	■	■	■	■	■
Bour et al. 2010 [70]	■	■	■	■	■	□	■	■
Kandiah et al. 2011 [23]	■	■	■	■	■	■	■	■
Allan et al. 2011 [24]	■	■	■	■	■	■	■	■
Planton et al. 2012 [71]	■	■	■	■	■	□	■	■
Kliper et al. 2013 [31]	■	■	■	■	■	■	■	■
Jacquin et al. 2014 [25]	■	■	■	■	■	■	■	■
Kliper et al. 2014 [32]	■	■	■	■	■	■	■	■
Benedictus et al. 2015 [26]	■	■	■	■	■	■	■	■
Wang et al. 2015 [72]	■	■	□	■	■	■	■	■
Yang et al. 2015 [49]	■	■	□	■	■	■	■	■
Akinyemi et al. 2015 [38]	□	■	■	■	■	■	■	■
Kumral et al. 2015 [50]	■	■	□	□	■	■	■	■
Narasimhalu et al. 2015 [39]	□	■	□	□	■	■	■	■
Yalbuzdag et al. 2015 [40]	□	■	□	□	□	■	■	■
Rezaei et al. 2016 [27]	■	■	■	■	■	■	■	■
Moulin et al. 2016 [4]	■	■	■	■	■	■	■	■
Auriel et al. 2016 [30]	■	■	■	■	■	■	■	■

Table 2 (continued)

	Recruitment of consecutive patients	Selection criteria of study population clearly described	Pre-stroke cognition analyzed by IQCODE or equivalent	Statement on inclusion or not of patients with pre-existing cognitive impairment	Post-stroke cognitive state diagnosed by standardized criteria	Adjustment on known predictors of post-stroke cognitive impairment	Standardized evaluation of biomarkers	Methodology detailed enough to allow replication
Kliper et al. 2016 [33]	■	■	■	■	■	■	■	■
Sivakumar et al. 2017 [51]	■	■	□	■	□	■	■	■
Suministrado et al. 2017 [62]	■	■	■	■	□	■	■	■
Arba et al. 2017 [53]	■	■	□	■	■	■	■	■
Sagnier et al. 2017 [63]	■	■	■	■	□	■	■	■
Ben Assayag et al. 2017 [28]	■	■	■	■	■	■	■	■
Ben Assayag et al. 2017 [29]	■	■	■	■	■	■	■	■
Molad et al. 2017 [34]	■	■	■	■	■	■	■	■
Arba et al. 2018 [52]	■	■	□	■	■	■	■	■
Benjamin et al. 2018 [54]	■	■	□	■	■	■	■	■
Guo et al. 2018 [55]	■	■	□	■	■	■	■	■
Yatawara et al. 2018 [41]	□	■	■	■	■	■	■	■
Zhao et al. 2018 [56]	■	■	□	□	■	■	■	■

Black squares represent studies fulfilling quality criteria and white squares studies not fulfilling quality criteria. IQCODE: Informant Questionnaire on Cognitive Decline in the Elderly

Haemorrhage

was found in three [36, 37, 65]. Cholesterol blood levels were evaluated in six articles [10, 14, 23, 46, 47, 50]. Most of the studies did not find any association between cholesterol levels and post-stroke cognitive decline [14, 23, 46, 47]. Only two studies found a statistical association. The first article found that both higher levels of low-density lipoprotein (LDL) cholesterol and lower levels of high-density lipoprotein (HDL) cholesterol were independently associated to post-stroke cognitive decline [50]. The second study was focused on total cholesterol level and authors did not adjust on confounders [10]. Triglycerides levels were studied only in four studies [10, 46, 47, 50]. Only one study found an association between baseline triglycerides levels and post-stroke cognitive decline, but association was not adjusted [10]. Angiotensin-converting enzyme (ACE) gene polymorphisms were evaluated in three studies [10, 13, 70], with inconsistent results: two studies were negative [10, 13], while one article reported the association between the DD genotype and cognitive functions [70]. Biological markers of renal impairment were studied in three articles [10, 28, 30]. In one of the studies, previous nephropathy was associated with post-stroke cognitive impairment, but renal function was estimated with creatinine levels alone [10]. Two studies conducted on the same cohort found an independent association between impaired renal function, defined as creatinine clearance < 60 ml/min and post-stroke cognitive impairment [28, 30]. C-reactive protein (CRP) was studied in three articles [31, 39, 55]. Only one article found an independent association with

Table 3 Imaging markers evaluated in the selected studies

	SI or lacunes	WMC	BMB	Glob A	MTLA	EPVS	IMT	Other
Tatemichi et al. 1990 [57]	☐	☐	☐	■	☐	☐	☐	Number of old infarcts
Loeb et al. 1992 [64]	☐	■	☐	■	☐	☐	☐	☐
Schmidt et al. 1993 [7]	☐	☐	☐	■	☐	☐	☐	Multiple brain infarcts
Bornstein et al. 1996 [8]	■	☐	☐	☐	☐	☐	☐	☐
Kase et al. 1998 [35]	■	■	☐	■	☐	☐	☐	☐
Pohjasvaara et al. 2000 [9]	☐	■	☐	■	■	☐	☐	☐
Barba et al. 2000 [10]	☐	☐	☐	☐	☐	☐	☐	☐
Henon et al. 2001 [11]	■	■	☐	■	☐	☐	☐	☐
Cordoliani et al. 2003 [12]	■	■	☐	■	■	☐	☐	☐
Arpa et al. 2003 [13]	☐	☐	☐	☐	☐	☐	☐	☐
Ballard et al. 2004 [65]	☐	☐	☐	☐	☐	☐	☐	☐
Rasquin et al. 2004 [14]	☐	■	☐	■	☐	☐	☐	☐
Mok et al. 2004 [58]	■	■	☐	☐	☐	☐	☐	☐
Ivan et al. 2004 [36]	☐	☐	☐	☐	☐	☐	☐	☐
Tang et al. 2004 [15]	■	■	☐	■	☐	☐	☐	☐
Talelli et al. 2004 [43]	☐	☐	☐	☐	☐	☐	■	Carotid plaques; ICA stenosis
Altieri et al. 2004 [16]	☐	■	☐	■	☐	☐	☐	☐
Klimkowicz et al. 2005 [17]	☐	☐	☐	☐	☐	☐	☐	☐
del Ser et al. 2005 [66]	☐	■	☐	■	■	☐	☐	☐
Mok et al. 2005 [59]	■	■	☐	■	■	☐	☐	☐
Appelros et al. 2005 [44]	☐	■	☐	☐	☐	☐	☐	☐
Martin-Ruiz et al. 2006 [60]	☐	☐	☐	☐	☐	☐	☐	☐
Sachdev et al. 2006 [67]	Unk	■	☐	■	☐	☐	☐	☐
Tang et al. 2006 [18]	☐	■	☐	■	☐	☐	☐	☐
Lee et al. 2007 [68]	☐	☐	☐	☐	☐	☐	■	☐
Pohjasvaara et al. 2007 [19]	☐	■	☐	■	■	☐	☐	☐
Thein et al. 2007 [45]	☐	■	☐	☐	☐	☐	☐	☐
Baum et al. 2007 [46]	☐	☐	☐	☐	☐	☐	☐	☐
Cordonnier et al. 2007 [20]	☐	■	☐	■	☐	☐	☐	☐
Stebbins et al. 2008 [21]	☐	■	☐	■	☐	☐	☐	☐
Tamam et al. 2008 [47]	☐	☐	☐	☐	☐	☐	☐	☐
Sachdev et al. 2009 [69]	☐	☐	☐	☐	☐	☐	☐	☐
Delgado et al. 2010 [61]	☐	■	☐	☐	☐	☐	☐	☐
Chausson et al. 2010 [48]	■	■	☐	☐	☐	☐	☐	☐
Wagle et al. 2010 [37]	☐	☐	☐	☐	☐	☐	☐	☐
Williamson et al. 2010 [22]	☐	☐	☐	☐	☐	☐	☐	☐
Bour et al. 2010 [70]	☐	☐	☐	☐	☐	☐	☐	☐
Kandiah et al. 2011 [23]	☐	■	☐	☐	☐	☐	☐	☐
Allan et al. 2011 [24]	☐	☐	☐	☐	☐	☐	☐	☐
Planton et al. 2012 [71]	☐	☐	☐	☐	☐	☐	☐	☐
Kliper et al. 2013 [31]	☐	■	☐	☐	☐	☐	☐	☐
Jacquin et al. 2014 [25]	■	■	☐	☐	☐	☐	☐	☐
Kliper et al. 2014 [32]	☐	☐	☐	☐	☐	☐	☐	☐
Benedictus et al. 2015 [26]	☐	■	■	■	☐	☐	☐	☐
Wang et al. 2015 [72]	☐	☐	■	☐	☐	☐	☐	☐
Yang et al. 2015 [49]	☐	■	☐	■	■	☐	☐	☐
Akinyemi et al. 2015 [38]	☐	■	☐	■	■	☐	☐	☐
Kumral et al. 2015 [50]	☐	■	☐	☐	☐	☐	☐	☐
Narasimhalu et al. 2015 [39]	☐	☐	☐	☐	☐	☐	☐	☐
Yalbuzdag et al. 2015 [40]	☐	☐	☐	☐	☐	☐	☐	☐

Table 3 (continued)

	SI or lacunes	WMC	BMB	Glob A	MTLA	EPVS	IMT	Other
Rezaei et al. 2016 [27]	□	□	□	□	□	□	□	□
Moulin et al. 2016 [4]	■	■	■	■	□	□	□	Superficial siderosis
Auriel et al. 2016 [30]	□	□	□	□	□	□	□	□
Kliper et al. 2016 [33]	□	□	□	□	□	□	□	Hippocampal mean diffusivity
Sivakumar et al. 2017 [51]	□	■	□	□	□	□	□	□
Suministrado et al. 2017 [62]	□	□	□	□	□	□	□	Hemodynamics on TCD
Arba et al. 2017 [53]	■	■	□	■	■	■	□	□
Sagnier et al. 2017 [63]	□	■	□	■	□	□	□	□
Ben Assayag et al. 2017 [28]	□	■	□	■	□	□	□	□
Ben Assayag et al. 2017 [29]	□	□	□	□	□	□	□	□
Molad et al. 2017 [34]	□	■	□	□	□	□	□	□
Arba et al. 2018 [52]	■	■	□	■	□	■	□	□
Benjamin et al. 2018 [54]	■	□	□	□	□	■	□	□
Guo et al. 2018 [55]	□	□	□	□	□	□	□	□
Yatawara et al. 2018 [41]	■	■	□	■	□	□	□	□
Zhao et al. 2018 [56]	□	□	□	□	□	□	□	WMC anatomical distribution

SI Silent infarcts*WMC* white matter changes, *BMB* brain microbleeds, *Glob A* global atrophy, *MTLA* Medial temporal lobe atrophy, *EPVS* enlarged perivascular spaces, *IMT* intima media thickness, *ICA* internal carotid artery, *TCD* Trans-cranial Doppler

post-stroke cognitive impairment [55]. Alpha-1 antichymotrypsin genotype was studied in two articles [13, 17]. Klimkowicz et al. found a significant association between alpha-1-antichymotrypsin genotype and post-stroke cognitive impairment [17], the prevalence of ACT-TT genotype and T-allele being higher in patients with post-stroke cognitive impairment. However, the other study did not find any significant association with genotype and allelic distribution of the polymorphisms [13]. Levels of glycated hemoglobin A1c (A1c) were studied in two articles: in one of them no significant association was found with post-stroke cognitive impairment [23], the other showed an independent association with higher glycated hemoglobin A1c (A1c) levels [28]. Homocystein levels were studied in two articles that did not find any association [10, 67]. Hematocrit levels were studied in two articles: both of the studies found an association in univariate analysis between hematocrit and post-stroke cognitive decline, but the association disappeared in the adjusted analysis [10, 31]. Following our research strategy, we did not identify any study on cerebro-spinal fluid biological biomarkers.

Discussion

Our study has shown that (i) 42 independent cohorts resulting in 66 articles, met the selection criteria (median number of 170 patients; median follow-up of 12 months); (ii) all studies met quality criteria for description of the study population and standardization of biomarkers included in the analysis; (iii) 29 out of 66 studies met all quality criteria; (iv) the most consistent predictors of cognitive impairment after stroke were global brain atrophy and medial temporal lobe atrophy; (v) there was no convincing evidence that any biological marker may predict cognitive impairment.

The strengths of this systematic review are the selection of studies on cohorts of patients recruited after a clinical stroke, i.e., sharing the profile of patients who are currently admitted in stroke units. We selected cohorts with a modern management of brain imaging, and with a cognitive evaluation carried out at least 3 months after stroke, to account for potential misdiagnoses.

Our study has also limitations concerning the generalizability of the results: only 17% of eligible studies included more than 300 patients and differences in the methods did not allow direct comparisons. In particular, heterogeneity of available measures leading to definition of pre-existing cognitive decline and dementia limit the comparisons among different studies with different designs. Actually, the prevalence of dementia in the same cohort varies according to diagnostic criteria. Indeed, according to Erkinjuntti et al., type of evaluation for the mentioned criteria (DSL-IIIR, DSM-IV, ICD10) may have led to great differences in prevalence of dementia, which could vary by a factor of ten in the number of subjects classified as having dementia [73]. Moreover, the median follow-up was 12 months, with 26% of studies with a 3-year follow-up. A cognitive follow-up limited to the early phase may dismiss late-onset cognitive impairment from the analysis of potential predictors,

leading to an important risk of misclassification of patients considered as cognitively normal although they may develop dementia a few months later.

Genetic and biochemical studies provided inconsistent results that may be explained by differences in sample sizes, case mix, duration of follow-up, and criteria used to define cognitive impairment. Associations with genetic polymorphisms were found only in studies that did not fulfill all quality criteria, leading to an important risk of false positive. Moreover, our research strategy identified only plasmatic biological markers, likely because of limitations in performing cerebro-spinal fluid studies in patients with acute stroke.

Overall, the presence of global cerebral atrophy was associated with the occurrence of cognitive impairment. The only studies that failed to find any relationship had small sample sizes [21, 35], or did not meet quality criteria such as consecutive recruitment of patients [35] or adjustment on confounders [35, 67]. The same holds true for medial temporal atrophy. The only study where medial temporal lobe atrophy did not predict cognitive impairment was not properly powered [59]. In only two studies that did not evaluate pre-stroke cognitively impaired patients [49, 52], cerebral atrophy was found as a predictor for post-stroke cognitive impairment. The first study did not find the association, in the second study the association disappeared after adjustment. Indeed, it is unlikely that cerebral atrophy could be a surrogate measure for pre-stroke dementia. When pre-stroke cognitive decline was evaluated with a standardized method, studies either did not include pre-stroke demented patients or adjusted variables on pre-stroke clinical evaluation. We found the same results for medial temporal lobe atrophy.

There was no convincing evidence of a relationship between the presence of silent infarcts or lacunes and development of cognitive impairment in the 14 independent studies that addressed this issue [4, 8, 11, 12, 15, 25, 35, 41, 48, 52–54, 58, 59]. The four studies that reported the association were either based on CT scans, where silent infarcts may be either missed or misdiagnosed [12, 25, 48], or conducted on a selected small vessels disease stroke population [54].

The association between white matter changes and cognitive impairment was found in most studies, but not in all. An important confounder, not always considered, is the coexistence of cerebral atrophy. Type of neuroimaging available (CT or MRI) and methods of evaluation of WMC were widely heterogeneous and potentially biased by stroke extension and location. Indeed, one major limitation in the quantification of extension of WMC is the inclusion of WMC ipsilateral to the acute lesion, therefore including changes that are related to acute stroke or to its consequences on the adjacent parenchyma. Most of the studies quantified WMC by modified Fakezas scale (in some cases with the support of user-assisted threshold based planimetric techniques) [9, 11, 12, 20, 23, 50, 51]. In other cases, white matter hyperintensities (WMH) were graded according to the Van Swieten scale from 0 to 4, combining the ratings in the anterior and posterior periventricular white matter [52, 53]. Other methods of evaluation were Fazekas and Schmidt rating scale [71]. Some studies detailed the localization of WMH in periventricular or deep [23]. One other study quantified WMC by rating on a four-point scale in five different brain regions of the right and left hemispheres separately, using the visual scale ‘age-related white matter changes’ (ARWMC) [61]. Leukoaraiosis was diagnosed in by subjective assessment by a neurologist or radiologist based on the presence of bilateral patchy or diffuse areas of hypodensity of the subcortical white matter of the brain on brain CT [45, 64]. Therefore, differences in methods of evaluation limited comparisons among studies.

The three studies that evaluated the association between brain microbleeds and post -stroke cognitive impairment, found a significant association [4, 26, 72]. However, these results need to be confirmed mainly because two of these studies were conducted in the same selected cohort of patients with spontaneous intracerebral haemorrhages [4, 26].

In conclusion, the results of this systematic review indicate that, in patients with an acute stroke, cerebral atrophy is the most consistent predictor of future cognitive impairment. It could be indicated to measure it in the acute phase of stroke to consider a cognitive follow-up for asymptomatic patients with cerebral atrophy. Future research should be performed on studies fulfilling well-defined standardized quality criteria, possibly with longer follow-up and larger cohorts of patients. Research should focus on markers that can be detected early in the stroke unit. MRI markers seem to be potential candidates and characterisation of lesion burden and location. The study of indirect MRI evidence of microstructural lesions should focus on promising predictors such as superficial siderosis, enlarged perivascular spaces, cortical thickness, stroke volume and cerebral microinfarcts.

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Compliance with ethical standards

Conflicts of interest B Casolla, F Caparros, C Cordonnier, S Bombois, H Hénon, R Bordet, F Orzi, and D Leys have no conflict of interest to report.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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