Magnetic resonance imaging and brain injury in the chronic phase after aneurysmal subarachnoid hemorrhage: A systematic review

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Abstract

Background: Case-fatality rates after aneurysmal subarachnoid hemorrhage have decreased over the past decades. However, many patients who survive an aneurysmal subarachnoid hemorrhage have long-term functional and cognitive impairments.

Aims: We sought to review all data on conventional brain MRI obtained in the chronic phase after aneurysmal subarachnoid hemorrhage to (1) analyze the proportion of patients with cerebral infarction or brain volume changes; (2) investigate baseline determinants predictive of MRI-detected damage; and (3) assess if brain damage is predictive of patient outcome.

Summary of review: All original data published between 1 January 2000 and 4 October 2017 was searched using the PUBMED, EMBASE, and Web of Science databases. Based on preset inclusion criteria, 15 from 5200 articles were included with a total of 996 aneurysmal subarachnoid hemorrhage patients. Quality assessment, risk of bias assessment, and level of evidence assessment were performed. The results according to aim, with levels of evidence, were: (1) 25 to 81% of aneurysmal subarachnoid hemorrhage patients show infarcts (strong); there is a higher ratio of cerebrospinal fluid-to-intracranial volume in patients compared to controls (strong); (2) there is a negative relation between age (moderate), DCI (low) and brain volume measurement outcomes; (3) lower brain parenchymal volume (strong) and the presence of infarcts or infarct volumes (moderate) are associated with a worse outcome.

Conclusion: Patients after aneurysmal subarachnoid hemorrhage may demonstrate brain infarcts and decreased brain parenchyma, which is related to worse outcome. Thereby, both brain infarcts and brain volume measurements could be used as outcome markers in pharmaceutical trials.

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Keywords
Subarachnoid hemorrhage, MRI, brain injury, cerebral infarction, volume measurements, radiology

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Introduction

Case-fatality rates after aneurysmal subarachnoid hemorrhage (aSAH) have decreased over the past decades. Today, approximately one-third of patients die within three months after the event.⁴ Of the patients who survive, many have long-term functional and cognitive impairments.²,³

Common determinants of poor functional outcome are the impact of the acute hemorrhage, also known as early brain injury (EBI),⁵,⁶ bleeding related acute ischemia,⁶,⁷ and complications such as rebleeding of the aneurysm, procedure-related complications,⁸,⁹ delayed
The following baseline characteristics were extracted: number of patients who received MR imaging, age, sex, clinical condition at admission, i.e., Hunt and Hess scale (H&H)\textsuperscript{18} or World Federation of Neurosurgical Societies SAH grading system (WFNS),\textsuperscript{19} amount of blood on admission CT, i.e., Hijdra scale\textsuperscript{20} or Fisher grade,\textsuperscript{21} type of aneurysm treatment, the timing of the MRI, MRI sequences, and field strength.

To address the first aim, data on the number of patients with a cerebral infarct were extracted, and the proportion (with 95% CI) of patients with an infarct was calculated. Additionally, the number of infarcts per patient and infarct size was extracted. As well, brain volume measurement results were extracted. Due to the heterogeneity of the used measurements, it was chosen to focus on the cerebrospinal fluid/intracranial volume ratio (CSF/ICV) or measures related to it, and on the ventricular-to-intracranial-width ratio (VIWr). The incorporated measures related to the CSF/ICV were brain parenchymal volume (BPV), lateral ventricle volume, and peripheral CSF volume.
To address the second aim, data on determinants and their relation to cerebral infarct or brain volume changes were extracted. The parameters investigated were: age, the clinical condition on admission, and the amount of extravasated blood on admission CT. For brain volume changes, two additional determinants could be investigated: preoperative- or symptomatic hydrocephalus, and DCI.

To address the third aim, data describing the relation between brain damage and neuropsychological or clinical outcome were extracted.

Statistical analyses were performed using SPSS Statistics (SPSS, Inc., Chicago, IL, version 22).

**Results**

The search strategy yielded 5200 unduplicated articles of which 15 were included (Figure 1). Of these 15 articles, two had an overlapping patient population, but different outcome measures. The articles totaled 996 aSAH patients with a median number of 55 per study (range 20–138). Four articles included control subjects with a median number of 30 subjects (range 25–30). For each study, study characteristics are presented in Supplemental Table 3. Seven out of the fifteen articles fulfilled the criteria for high-quality studies. Levels of evidence of the findings described below are presented in Table 1.

**Proportion of aSAH patients with cerebral infarction or brain volume changes**

**Cerebral infarction.** Twelve studies, with a median number of 50 patients per study (range 20–138), reported on the presence of cerebral infarcts. Of 791 patients, 372 showed a cerebral infarct.
The percentage of patients with an infarct ranged between 25 and 81 percent between studies (see Supplemental Table 3). The included studies varied in patient disease severity between WFNS I or II at admission or H&H grade 1 up to 4.31,36 One study reported on the number of infarcts detected in the patients who demonstrated infarcts: 152 infarcts in 84 patients.31 Six studies reported on the size of the infarcts.25,26,28,29,32,35 Three studies used a volume measurement (ml or cm$^3$) and found a mean volume of 8.6–43.4 ml in a total of 108 patients.25,28,35 The other three studies reported the mean diameter of the deficit, which ranged from 19 mm to 57 mm in a total of 102 patients.26,29,32 These results are shown in Table 2.

**Brain volume changes.** Six articles, with a median number of 65.5 patients per study (range 38-88), reported on brain volume changes.22,24,25,29,35 In four of the six articles, patients were compared to age- and sex-matched controls.22,24,35 Two articles reported on the CSF/ICV ratio,22,24 and in two other articles the CSF/ICV could be calculated.25,35 The results (Table 3) show that CSF/ICV ratios were significantly higher in patients compared to controls for two out of three studies,22,24 while there was no difference in the third.35 The third studies' control group partly consisted of individuals who underwent endovascular intervention for a non-ruptured aneurysm.35

Three articles reported the VIWr (Table 3).23,24,29 Two studies found a significant higher mean ratio in aSAH patients compared to controls,23,24 The third study reported results found in endovascular- and surgical-treated patients.29

**Baseline determinants predictive of MRI-detected damage**

**Determinants of cerebral infarction.** Table 4 summarizes the results found on this topic. In short, 2 studies, with 38 and 88 patients, addressed this subject.25,29 Clinical condition at admission was found not to relate to presence of cerebral infarct or infarct volumes (descriptive analysis).25 One study found no relation between the amount of extravasated blood on admission CT and the presence of cerebral infarcts or infarct volumes (descriptive analysis),25 while the second study did find a significant association with a higher Fisher grade. More specifically, a higher Fisher grade was associated with an increased number of infarcts outside the territory of the parental artery of the aneurysm ($p = 0.001$).29

**Determinants of brain volume changes.** Table 4 summarizes the results found on this topic. In short, three studies, with a median of 76 patients (range 38–77), reported on this subject.23–25 A significant correlation of age with brain volume changes was found in two studies (CSF/ICV: $r = 0.718$, $p < 0.001$; CSF/ICV: $r = 0.416$, $p < 0.001$; VIWr: $r = 0.366$, $p = 0.001$).23,24

No relation between clinical grade at admission and brain volume changes was found in two studies (CSF/ICV: $p = 0.239$; BPV: B (95%CI): 3.2 ($-5$ – $12.1$)).24,25 One study on the other hand, did find more brain atrophy in patients with higher H&H grade (VIWr: $p < 0.001$).24

The amount of extravasated blood on admission CT was found to be associated with brain atrophy in one study (CSF/ICV: $p = 0.014$; VIWr: $p = 0.001$),24 whereas another did not find a relation (BPV: B (95% CI): 0.35 ($-0.71$ – $1.46$)).25 One research group reported that patients with hydrocephalus on admission CT tended to have lower

### Table 1. Level of evidence

| Statement                                      | Level of evidence |
|------------------------------------------------|-------------------|
| Brain damage – Cerebral infarct                | Strong            |
| 25–81% of patients showed an cerebral infarct on MRI in the chronic phase after aSAH | Strong            |
| Brain damage – Volume measurements             | Strong            |
| There was a significant difference in brain volume measurements between patients and controls | Strong            |
| Determinants of volume changes                 | Moderate          |
| Patient age was significantly correlated with a higher CSF/ICV and VIWr | Moderate          |
| DCI was found to be related to smaller brain parenchymal volumes and lateral ventricle enlargement | Low               |
| Brain damage and clinical or neuropsychological outcome – Cerebral infarct | Moderate          |
| The presence of infarcts or infarct volumes was significantly correlated with clinical and neuropsychological outcome | Moderate          |
| Brain damage and neuropsychological or clinical outcome – Volume measurements | Strong            |
| Brain parenchymal volume measurements and VIWr were related to clinical and neuropsychological outcome | Strong            |
brain volumes (CSF/ICV: $p = 0.51$; VIWr: $p < 0.001$). Another study reported that symptomatic hydrocephalus was not related to volume measurements (BPV: B (95% CI): $-14 (-38 - 10)$; lateral ventricle volume: B (95% CI) $0.18 (-0.29 - 0.66)$).

Lastly, it was reported that DCI is related to lower BPVs and lateral ventricle enlargement, which would result in a higher CSF/ICV (B (95% CI): $-38 (-66 - -9)$; B (95% CI): $0.80 (0.26 - 1.35)$).

Table 2. Size of the deficits in patients with a cerebral infarct

| Study               | No.       | Mean volume of infarct (ml/cm³) | SD  | Mean diameter of infarct (mm) | SD  |
|---------------------|-----------|---------------------------------|-----|-------------------------------|-----|
| Bendel et al.²⁸     | 15/67ᵃ    | 17.6                            | 35.8|                               |     |
|                     | 33/71     | 20.9                            | 46.5|                               |     |
|                     | 7/67      | 27.6                            | 26.3|                               |     |
|                     | 11/71     | 43.4                            | 69.7|                               |     |
| De Bresser et al.³⁵ | 26/55     | 8.7ᵇ                            | 0.4 – 61.³ᵇ |                              |     |
| De Bresser et al.²⁵ | 16/38     | 8.6ᵇ                            | 1.1 – 80.⁹ᵇ |                              |     |
| Koivisto et al.²⁹   | 8/40ᵃ     | 43                              | 40  |                               |     |
|                     | 21/47     | 36                              | 31  |                               |     |
|                     | 9/40      | 30                              | 29  |                               |     |
|                     | 8/47      | 52                              | 30  |                               |     |
| Koivisto et al.³²   | 6/19ᵈ     | 19ᵈ                            | 13  |                               |     |
|                     | 7/21      | 57                              | 42  |                               |     |
| Soppi et al.²⁶      | 21/62ᵃ    | 39.3                            | 27  |                               |     |
|                     | 22/64     | 34.3                            | 28  |                               |     |

Note: In the articles it was not specified if, in case of multiple infarcts, a summation of the volumes or sizes was given or results of the largest infarct were given, unless stated otherwise.

No.: number of patients with an infarct / total MR population.

ᵃResults were presented based on vascular territory and treatment method (i.e. coiling or clipping), in descending order; infarcts in parental artery territory in coiled aSAH patients, infarcts in parental artery territory in clipped aSAH patients, infarct in vascular territories other than the parental territory in coiled aSAH patients, and infarcts in vascular territories other than the parental territory in clipped aSAH patients.

ᵇMedian and 10th–90th percentile.

ᵈPatients presented by treatment method: surgical and endovascular.

ᵈSize of infarction is size of largest deficit in case of multiple deficits.

ᵃPatients presented by treatment strategy: enteral and intravenous administration of nimodipine.

Damage detected on MRI predictive of patient outcome

Clinical or neuropsychological outcome – Cerebral infarct. Table 5 shows all results on this topic. Two studies, with 32 and 88 patients, reported on the relation between presence of a cerebral infarct and clinical outcome.

An infarct ($p < 0.05$), an infarct in the parental artery territory of the aneurysm ($p < 0.003$) or in another vascular territory ($p = 0.003$) was associated with worse clinical outcome. Logistic regression analysis proved an infarct in the parental artery territory of the ruptured aneurysm to be an independent predictor of poorer clinical outcome (OR 6.20; 95% CI 1.67–23.05; $p = 0.006$).

Two studies, with 88 and 138 patients, reported on the relation of infarct size and outcome. Size of infarcts in the parental artery territory ($p < 0.001$) or in another vascular territory ($p = 0.001$), was significantly associated with poorer clinical outcome. A significant relation between infarct volume and deficits in several tests of visual reproduction, delayed story recall, performance intelligent quotient and verbal intelligence quotient was reported (most $p$-values < 0.01).
Clinical or neuropsychological outcome – Brain volume measurements. Table 5 shows all results on this topic.

In short, four studies with a median of 65.5 patients (range 38–88) reported on correlations between brain volume measurements and clinical outcome.24,25,29,35

The reported relations were as follows; a positive relation for BPV (at 6 /2 months OR 38.8, 95% CI 4.6–329.0; and at 18 months OR 91.2, 95% CI 2.5–3395.1),25,35 a positive relation for VIWr (GOS 2–4 vs. 5; 0.28 /2 0.06 vs. 0.23 /2 0.06, p = 0.028 and univariate analysis, p = 0.04),24,29 a positive relation for lateral ventricle volume (OR 7.4, 95% CI 1.6–33.5),35 no relation for lateral ventricle volume (OR 1.1; 95% CI 0.2–5.1),35 and no relation for peripheral CSF volume (OR 2.3, 95% CI, 0.6–8.0).35 Sample size differences between the studies investigating the relation between lateral ventricle volume and outcome may have contributed to conflicting differences; the sample size was 55 in the study where a positive relation was found compared to 38 in the negative study.

Two studies, with 37 and 76 patients, reported on brain volume measures and neuropsychological outcome.22,24 In short, there was a positive relationship and a tendency towards a positive relationship between CSF/ICV and neurologic deficits (present vs. absent; 37.45 ± 6.13 vs. 32.66 ± 7.25, p = 0.003 and 42.0 ± 3.6 vs. 40.4 ± 3.5, non-significant).22,24 A higher VIWr was found in patients with any neuropsychological deficit (present vs. absent; 0.25 ± 0.07 vs. 0.21 ± 0.05, p = 0.028), especially with a deficit in general intellectual functioning (present vs. absent; 0.30 ± 0.04 vs. 0.22 ± 0.06, p < 0.001).24

Discussion

The following findings, summarized according to the aims of the review, were found: (1) 25–81% of aSAH patients show infarcts; there is a higher ratio of cerebrospinal fluid-to-intracranial volume in patients compared to controls; (2) there is a negative relation between age and DCI versus brain volume measurement outcomes; (3) lower BPV and the presence of infarcts or infarct volumes are associated with a worse outcome.

The wide range (25–81%) in aSAH patients demonstrating brain infarcts (strong level of evidence) underscores the heterogeneity of patient populations in the included articles. Regarding brain volume changes, it was found that aSAH patients have a lower brain volume compared to controls (strong level of evidence).22–24 Unfortunately, due to the continuous nature of a volume measurement and the effect of age on such a measurement, a cut-off value for presence or absence of brain volume loss could not be established. Therefore, the proportion of aSAH patients with brain volume loss could not be calculated. However, in general, the decreased brain volume in aSAH patients as compared to controls does bring support for the EBI theory. Further support for the EBI theory is found in two of the studies included in this review. One study found brain atrophy independent of infarct presence,22 and a second study quantified global ventricular and sulcal enlargement.24

Regarding the question whether there are determinants predictive of MRI-detected damage, our search...
### Table 4. Determinants of cerebral infarcts and brain volume measurements

| Determinant – Cerebral infarcts | Study | Outcome (statistics) |
|---------------------------------|-------|----------------------|
| Age                             | –     | –                    |
| **Clinical condition at admission** | De Bresser et al. 25 | Not related to the presence of infarcts or infarct volumes (descriptive analysis) |
| **Amount of extravasated blood** | De Bresser et al. 25 | Not related to the presence of infarcts or infarct volumes (statistics not given) |
| Koivisto et al. 29 | Higher Fisher grade is associated with increased number of infarcts outside the territory of the parental artery of the aneurysm ($p = 0.001$) |

| Determinant – Brain volume measurement | Study | Measure | Outcome (statistics) |
|---------------------------------------|-------|---------|----------------------|
| Age                                   | Bendel et al. 24 | CSF/ICV | Significant correlation with a higher ratio ($r = 0.781$, $p < 0.001$) |
| Bendel et al. 24 | VIWr | Significant correlation with a higher ratio ($r = 0.416$, $p < 0.001$) |
| Bendel et al. 23 | VIWr | Significant correlation with a higher ratio ($r = 0.366$, $p = 0.001$) |
| **Clinical condition at admission** | Bendel et al. 24 | CSF/ICV | No relation at 12 months (H&H grade 1–2: 43.98 ± 7.54 vs. H&H grade 3–5: 37.15 ± 5.18; $p = 0.239$) |
| De Bresser et al. 25 | BPV | No relation at 18 months (B, 95% CI: 3.2, —5—12.1) |
| Bendel et al. 24 | VIWr | Higher H&H grade is related to higher ratio (H&H 1–2: 0.21 ± 0.06 vs. H&H 3–5: 0.29 ± 0.06, $p < 0.001$) |
| **Amount of extravasated blood** | Bendel et al. 24 | CSF/ICV | Associated with a higher ratio (Fisher grade 0–2: 32.75 ± 7.75 vs Fisher grade 3–4: 37.13 ± 6.10, $p = 0.014$) |
| Bendel et al. 24 | VIWr | Associated with a higher ratio (grade 0–2: 0.20 ± 0.06 vs. grade 3–4: 0.25 ± 0.06, $p = 0.001$). |
| De Bresser et al. 25 | BPV | No relation with Hijdra score (B, 95% CI: 0.38, —0.71—1.46) |
| **Hydrocephalus** | Bendel et al. 24 | CSF/ICV | Tends to be related (hydrocephalus: 34.44 ± 7.57 vs. no hydrocephalus: 37.64 ± 5.35, $p = 0.51$) |
| Bendel et al. 24 | VIWr | Significant correlation (hydrocephalus: 0.28 ± 0.06 vs. no hydrocephalus: 0.21 ± 0.06, $p < 0.001$) |
| De Bresser et al. 25 | BPV | Not related (B, 95% CI: —14, —38—10) |
| **Lateral ventricle volume** | De Bresser et al. 25 | BPV | Related to smaller volumes (B, 95% CI: —38, —66—9) |
| **DCI** | De Bresser et al. 25 | BPV | Related to lateral ventricle enlargement (B, 95% CI: 0.80, 0.26—1.35) |

*aPreoperative hydrocephalus on admission CT.*

*bSymptomatic hydrocephalus defined as a decreased level of consciousness with increased bicaudate index that was larger than the upper 95th percentile for age.*

*cDefined as new focal deficits during admission or decreasing level of consciousness with new infarcts on CT.*

CSF/ICV: cerebrospinal fluid/intracranial volume; VIWr: ventricular-to-intracranial width ratio; BPV: brain parenchymal volume; DCI: delayed cerebral ischemia.
taught us that a patient’s age is negatively related to brain volume (moderate level of evidence), and that DCI relates to smaller BPV and lateral ventricle enlargement (low level of evidence). The first, although yielding limited evidence, is not surprising. It is well known that some quantity of brain volume loss is encountered with increasing age. The second finding could be attributed to two things. One, in the study investigating this topic, the presence of new infarcts was included in their DCI definition. Logically, this

| Table 5. MRI damage predictive of patient outcome |
|--------------------------------------------------|
| Infarction and patient outcome                    |
| Study                                            | Outcome (statistics)                                      |
| Infarct presence                                 | Infarct presence was related to poorer clinical outcome (p < 0.05) |
| Pysalo et al.                                    | Infarct presence within (p < 0.003) or outside the parental artery territory (p = 0.003) was associated with poorer clinical outcome Infarct in the parental artery territory of the aneurysm was an independent predictor of poorer clinical outcome (OR 6.20, 95% CI 1.67–23.05; p = 0.006, logistic regression) |
| Koivisto et al.                                  | Size of infarct within (p < 0.001) or outside the parental artery territory (p = 0.001) was associated with poorer clinical outcome |
| Infarct volume                                   | Relation between infarct volumes and tests of visual reproduction, delayed story recall, performance intelligent quotient and verbal intelligence quotient (13 of 17 tests showed significant correlation, with most p-values < 0.01) |
| Bendel et al.                                    | Size of infarct within (p < 0.001) or outside the parental artery territory (p = 0.001) was associated with poorer clinical outcome |

| Brain volume measures and patient outcome        |
| Measure                                          | Study                                            | Outcome (statistics)                                      |
| CSF/ICV                                         | Bendel et al.                                   | A significant higher ratio was found in patients with a neurologic deficit (present: 37.45 ± 6.13 vs. absent: 32.66 ± 7.25, p = 0.003) |
|                                                 | Bendel et al.                                   | In patients with at least one neuropsychological deficit, there was a trend towards a slightly higher ratio compared to patients without a deficit (present: 42.0 ± 3.6 vs. absent: 40.4 ± 3.5, non-significant) |
| VIWr                                            | Bendel et al.                                   | A higher ratio was found in patients with a lower GOS or patients with a neuropsychological deficit (GOS 2–4 vs. 5: 0.28 ± 0.06 vs. 0.23 ± 0.06, p = 0.028 and deficit present vs. absent: 0.25 ± 0.07 vs. 0.21 ± 0.05, p = 0.028) Especially with a deficit in general intellectual functioning (present vs. absent: 0.30 ± 0.04 vs. 0.22 ± 0.06, p < 0.001) |
|                                                 | Koivisto et al.                                 | Relation between higher ratio and poorer clinical outcome (GOS) (p = 0.04) |
| BPV                                             | De Bresser et al.                               | Lower volume 6 months after ictus was associated with worse outcome (mRS) (OR 38.8, 95% CI 4.6–329.0) |
|                                                 | De Bresser et al.                               | Lower BPV at 18 months after ictus was associated with worse outcome (mRS) (OR 91.2, 95% CI 2.5–3395.1) |
| Ventricle volume                                | De Bresser et al.                               | Higher lateral ventricle volume 6 months after ictus was associated with worse clinical outcome (mRS) (OR 7.4, 95% CI, 1.6–33.5) |
|                                                 | De Bresser et al.                               | No association was found between lateral ventricle volume at 18 months after ictus and outcome (mRS) (OR 1.1, 95% CI 0.2–5.1) |
| Peripheral CSF volume                           | De Bresser et al.                               | Higher peripheral CSF volume 6 months after ictus was not associated with outcome (mRS) (OR 2.3, 95% CI 0.6–8.0) |

*Variables used in the model: size of the ischemic lesion in the parental artery territory or in any other location; presence of an ischemic lesion in the parental artery territory or in any other location; deficit due to preoperative intracerebral hematoma and higher VIWr. CSF/ICV: cerebrospinal fluid/intracranial volume; VIWr: ventricular-to-intracranial width ratio; mRS: modified Rankin Scale; GOS: Glasgow outcome scale.*
would lead to a negative relation of DCI with brain volume due to volume loss within the infarcted area. Two, pronounced EBI, resulting in an increase of global parenchymal loss, may increase the likelihood of developing DCI. Besides the relation of age and DCI with MRI-detected damage, we were not able to identify any other positive or negative determinant. In fact, most investigated determinants produced conflicting results. This may be due to heterogeneity of the used research methods. Across studies, different tools or scoring systems were used for both determinants and outcome measures which made the results difficult to summarize and may have introduced inadequacies. For example, two scoring methods were used to assess the amount of extravasated blood, i.e. Fisher grade and Hijdra scale. Of these two, the Hijdra score is thought to be more precise since it takes into account specific anatomic locations and it is shown to have a better interobserver agreement than the Fisher scale. The same accounts for the discrepancies in findings between CFS/ICV and VIWt. In general the laborious volume measurements are thought to be more precise than the simple planimetric measure of the VIWt.

Our assessment of the relationship between MRI-detected damage and patient outcome, resulted in the findings that BPV and VIWt are related to clinical- and neuropsychological outcome (strong level of evidence), and that the presence of infarcts or infarct volumes are significantly correlated with clinical or neuropsychological outcome (moderate level of evidence). This latter finding is not surprising, since neurologic deficits are expected when infarcts occur in critical brain areas. It is known that tests may be difficult to perform in aSAH patients due to test difficulty, poor clinical condition, or severe headache during mental exercise. Therefore, studies investigating these properties may be skewed towards patients with better clinical outcome due to selection bias. Furthermore, a simple clinical tool such as the GOS can underappreciate the neuropsychological impact due to the gross subdivision into categories. For instance, patients with GOS “5” (i.e. mild or no disability) might still have subtle cognitive deficits and a need to apply adaptive strategies in daily life.

A limitation of this review is that only cerebral infarcts and brain volume changes were investigated. Not only infarcts but also many different focal injury entities can occur, including white matter lesions, superficial siderosis, and leukoaraiosis. Taking these lesions into account might lead to stronger levels of evidence. However, the manner of data presentation in the included studies did not allow for a thorough evaluation of this. Another limitation is that most studies showed skewedness towards a good recovery for the included patients. This is probably caused by the fact that patients had to endure scanning sessions and other follow-up investigations to be able to participate. Moreover, a few studies used data of MRI-sequences which were only obtained when the patient voluntarily stayed longer in the scanner, resulting in selection bias. As well, a few studies even stated a good clinical condition or functional recovery as a inclusion criterium. Thereby, it is likely that the general patient outcome in clinical practice, and thereby most likely the MRI results, is worse than the presented results.

Future directions

The findings of this review are relevant as they underscore that not only focal brain injury plays an important role in the course of the disease, but presumably EBI also attributes significantly to brain damage as was proven by brain volume loss irrespective of brain infarcts. The results regarding possible determinants of infarct development or brain volume loss, and the relation between brain damage and neuropsychological or clinical outcome, however, were scarce and heterogeneous. On the one hand, this shows the complexity of the effects of the disease with research focusing on different parameters, while on the other hand, it emphasizes the need to conduct research on a uniform basis to be able to draw solid conclusions.

Therefore, in future work the entity of EBI, its effect on volume changes and, in continuation, its effect on patient outcome should be investigated. Of equal importance is the question how to intervene in this process to constrain global neuronal loss. In addition, standardized research needs to be conducted to draw rigid conclusions regarding determinants of brain injury and/or brain volume measurement outcomes, and the relation with clinical- or neuropsychological outcome. Only when understanding the source of the damage and the subsequent effects on patient level, therapies can be targeted to prevent any additional damage and with that improve patient outcome.

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