Radiological Investigation of Spontaneous Intracerebral Hemorrhage
Systematic Review and Trinational Survey

Charlotte Cordonnier, MD, PhD; Catharina J.M. Klijn, MD, PhD; Janneke van Beijnum, MD; Rustam Al-Shahi Salman, MA, PhD, FRCP Edin

Background and Purpose—It is not always clear whether, how, and when to undertake further radiological investigation of spontaneous (nontraumatic) intracerebral hemorrhage (ICH).

Methods—We systematically reviewed Ovid MEDLINE and EMBASE databases for studies of the diagnostic utility of radiological investigations of the cause(s) of ICH. We sent a structured survey to neurologists, stroke specialists, neurosurgeons, and neuroradiologists in the United Kingdom, the Netherlands, and France to assess whether, how, and when they would investigate supratentorial ICH.

Results—This systematic review detected 20 relevant studies (including 1933 patients), which either quantified the yield of a radiological investigation/imaging strategy (n=15) or compared 2 imaging techniques (n=5). Six hundred ninety-two (49%) physicians responded to the survey. Further investigation would have been undertaken by the following: 99% of respondents, for younger (38 to 43 years), normotensive adults with lobar or deep ICH; 76%, for older (age 72 to 83 years), normotensive adults with deep ICH; and 31%, for older adults with deep ICH and prestroke hypertension. Younger patient age was the strongest influence on the decision to further investigate ICH (odds ratio=16; 95% confidence interval, 13 to 20), followed by the absence of prestroke hypertension (odds ratio=5; 95% confidence interval, 4 to 6) and lobar ICH location (odds ratio=2; 95% confidence interval, 1 to 2).

Conclusions—The paucity of studies on the diagnostic utility of imaging investigations of the cause(s) of ICH may contribute to the variation observed in when and how and which patients are investigated in current clinical practice. Studies comparing different types of diagnostic strategies are required. (Stroke. 2010;41:685-690.)

Key Words: intracerebral hemorrhage ▪ imaging ▪ etiology ▪ systematic review ▪ survey

Swift diagnosis of the underlying cause of intracerebral hemorrhage (ICH) directs treatment to improve outcome or prevent recurrent ICH.1 In current clinical practice, physicians seem to attribute the cause of ICH on the basis of a history suggestive of particular causes, the presence of associated risk factors, or the detection of underlying structural abnormalities.2 Decisions about whether and how to use radiological investigations other than computed tomography (CT) to determine ICH cause seem to be based on 3 principal factors: patient age, ICH location, and the existence of prestroke systemic arterial hypertension.3,4

Some studies have suggested that patients with putaminal hemorrhages should not routinely undergo cerebral angiography5 or that diagnostic cerebral angiography should not be considered in patients with spontaneous ICH who are older than 45 years and have preexisting hypertension and thalamic, putaminal, or posterior fossa ICH.4 Others have argued that the decision to investigate a patient with ICH should be primarily based on the patient’s clinical condition rather than on the site of the hemorrhage.3 This strategy is supported by the observation that the association between high blood pressure and deep (as opposed to lobar) ICH is only modest.6

Because the recommendations of the American Heart Association and European Stroke Organization on the investigation of ICH are based on low levels of evidence,7,8 we systematically reviewed the literature to investigate the diagnostic utility of radiological techniques performed after initial axial, unenhanced CT to identify structural abnormalities underlying ICH. In addition, we assessed everyday clinical practice by a survey of members of professional organizations involved in the investigation of patients with ICH in 3 European countries.
Methods

Systematic Literature Review

Literature Search Strategy

One reviewer (C.C.) searched Ovid MEDLINE from 1966 and EMBASE from 1980 to April 25, 2007, by using an 8-line electronic search strategy (supplemental Figure I, available online at http://stroke.ahajournals.org), supplemented by the authors’ personal files, manually searching the bibliographies of articles retrieved by the electronic search, and surveillance of relevant journals’ electronic tables of contents. We restricted this review to published data but not to language of publication. Titles and abstracts of retrieved citations were screened by C.C., and potentially suitable studies were read in full by C.C. and R.A.-S.S., who extracted relevant data and resolved disagreements by discussion.

Critical Appraisal

Guided by a checklist of ideal characteristics for a study of radiological investigation based on the principles of the QUality Assessment of Diagnostic Accuracy Studies9 and Standards for the Reporting of Diagnostic accuracy studies10 we sought generalizable study populations (representative of the spectrum of people who survive ICH to reach hospital) and 3 different study designs: (1) the yield of 1 investigation after ICH onset; (2) the yield of a predefined investigation strategy systematically applied after ICH onset (eg, 1 investigation or a sequence of investigations, determined by radiological and/or clinical groupings of ICH); and (3) comparison of 1 radiological technique against another radiological technique, or pathological examination after ICH onset, ideally with the readers blinded to demographic data and the results of the other investigation under study.

Data Extraction and Statistical Analysis

We extracted the numbers of underlying structural abnormalities in total and in subgroups (by age, prestroke hypertension, and ICH location) in categories (1) and (2) in the previous paragraph and the sensitivity, specificity, and predictive values of radiological investigation based on the principles of the QUality Assessment of Diagnostic Accuracy Studies9 and Standards for the Reporting of Diagnostic accuracy studies10 we sought generalizable study populations (representative of the spectrum of people who survive ICH to reach hospital) and 3 different study designs: (1) the yield of 1 investigation after ICH onset; (2) the yield of a predefined investigation strategy systematically applied after ICH onset (eg, 1 investigation or a sequence of investigations, determined by radiological and/or clinical groupings of ICH); and (3) comparison of 1 radiological technique against another radiological technique, or pathological examination after ICH onset, ideally with the readers blinded to demographic data and the results of the other investigation under study.

Trinational Survey of Professional Organizations

Survey Design

We sent by post a structured questionnaire (supplemental Figure II, available online at http://stroke.ahajournals.org) with 8 case vignettes that differed in terms of the following characteristics: ICH location (lobar or deep); prestroke hypertension (present or absent); and age (4 cases were <45 years [38, 39, 41, and 43 years of age] and 4 cases were >45 years [72, 75, 80, and 83 years of age]). We identified the survey target group from the professional organizations for stroke specialists, neurologists, neurosurgeons, and neuroradiologists in France, the United Kingdom, and the Netherlands (supplemental Figure III, available online at http://stroke.ahajournals.org). We determined the number of questionnaire recipients in each country (France=570, United Kingdom=568, and Netherlands=272) by identifying the smallest of its professional societies and taking an equal random sample of the membership of each of the country’s other societies. We sent nonresponders a reminder 3 months later.

Statistical Analyses

We restricted analyses to responders who confirmed that they were involved in the investigation of adults with ICH. We grouped respondents into their primary professional affiliation. Stroke specialists were neurologists in the Netherlands and France but tended to be general physicians in the United Kingdom. We grouped investigations on the basis of the techniques used: CT (CT angiography and CT venography), magnetic resonance (magnetic resonance imaging [MRI], magnetic resonance angiography [MRA], and MR venography), and intra-arterial digital subtraction angiography (IADSA). We calculated proportions, $\chi^2$ values, and univariable odds ratios with SPSS version 14.0 and calculated 95% confidence intervals (CIs) with Confidence Interval Analysis software.11 We did not perform multivariable analyses because each respondent rated the 8 scenarios (some of which possessed similar characteristics of interest), and therefore, the statistical assumption of independence was not met.

Results

Systematic Literature Review

The electronic searches of MEDLINE and EMBASE detected 5269 articles, of which 20 studies involving 1933 patients were suitable for inclusion. Twelve studies described the yield of a single investigation.5,5,12–21 Investigation yield was mostly concerned with IADSA,4,5,12–14,17,18,21 but 1 study concentrated on CT angiography20 and 3, on MRI.15,16,19 Three nonrandomized studies described the yield of strategies of delaying IADSA3,22 or of IADSA or CT/MRA for putaminal hemorrhage.23 The 5 remaining studies compared 1 investigation for the identification of ICH cause against another, without blinding the readers.24–28

Critical Appraisal

Generalizability of some studies was limited by their inclusion of a few patients with pure subdural,4,21 pure subarachnoid,16,20,21 or pure intraventricular5,5,17,18,21 hemorrhage. Most studies were affected by selection bias because they were retrospective assessments of how hospitalized patients with ICH had been investigated in everyday clinical practice (usually at tertiary referral centers, in neurosurgical units) with 1 exception.5 Few studies enrolled consecutive patients,3,22 because either they were undergoing an investigation (and were well enough to do so) or the ICH location was a determinant of the patient’s inclusion. The proportions of cohorts investigated ranged from 23% undergoing MRI after hospital admission19 to 65% undergoing immediate or delayed IADSA after hospital admission.3 Participants were often further selected for investigation by age,18 the location of their ICH,1,2,2,23,25 or whether the ICH extended into intraventricular, subdural, or subarachnoid compartments.12 Only 4 studies standardized the timing of the investigation.14,17,22,26 Most of the studies were performed in the 1980s and 1990s; since then, IADSA and MRI technology and availability have improved. Furthermore, IADSA did not always include selective injections of all vascular territories. In the studies involving MRI, magnet strength was 0.5 T15 or 1.5 T.16,19,28 One study mentioned that T2* gradient-recalled echo sequences were used when appropriate,16 and the other 4 did not use T2* gradient-recalled echo sequences.15,19,22,28 One study did not mention the type of MRI used for follow-up.22

Yield of 1 Investigation

Twelve studies described the yield of 1 investigation.4,5,12–21 Some of these studies contributed to the total of 726 patients with ICH in whom it was possible to calculate the yield of
Table 1. Prevalence and 95% CIs of AVMs and Aneurysms Based on 9 Studies in Which 726 Patients With ICH Were Investigated With Catheter Angiography

<table>
<thead>
<tr>
<th>Location†</th>
<th>AVMs</th>
<th>Aneurysms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>20</td>
<td>13</td>
</tr>
<tr>
<td>Age*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Young (&lt;50 y)</td>
<td>27</td>
<td>30</td>
</tr>
<tr>
<td>Old (≥50 y)</td>
<td>18</td>
<td>20</td>
</tr>
<tr>
<td>Blood pressure†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertensive</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Normotensive</td>
<td>28</td>
<td>13</td>
</tr>
<tr>
<td>Location‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lobar</td>
<td>31</td>
<td>20</td>
</tr>
<tr>
<td>Deep</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>Posterior fossa</td>
<td>37</td>
<td>0</td>
</tr>
</tbody>
</table>

*Data available for 3 studies including 249 patients.
†Data available for 6 studies including 578 patients.
‡Data available for 6 studies including 382 patients.

IADSA for finding an aneurysm or arteriovenous malformation (AVM) as the cause of the ICH.3,4,14,17,18,21,25,28 The prevalence of underlying AVMs was 20% (95% CI, 17 to 23) and of aneurysms, 13% (95% CI, 11 to 16; Table 1). Sex of the patients did not appear to influence yield in the individual studies, but the pooled results showed that the yield was relatively low in patients with prestroke hypertension and in those with a deep ICH location (Table 1).

**Yield of a Strategy**

Three studies described the yield of a strategy for investigating ICH.3,22,23 One study identified consecutive admissions with ICH and compared 2 prespecified approaches to IADSA timing: the prevalence of underlying abnormalities ranged from 24%, when an underlying abnormality had not been suspected and IADSA was postponed until 3 months after ICH, to 75%, when it had and IADSA was done in the acute phase and, if negative, repeated 3 months thereafter. A study of repeat IADSA for the investigation of subcortical lobar ICH when the initial IADSA had been negative yielded an 18% AVM detection rate.22 A study of 62 patients with putaminal ICH, by CT/MRA to investigate hypertensive patients age >60 years and by IADSA for everyone else, with follow-up MRA if the initial investigation was negative, found 9 patients (15%) with an angiographic abnormality; the yield was higher in normotensive patients and in those age ≤55 years.23

**Diagnostic Utility of Radiological Techniques**

Five studies compared a radiological technique against a reference standard (either another radiological technique, or operative or pathological findings) for identifying any structural abnormality underlying the ICH.24–28 In 1 study, individual data could not be extracted.27 The 4 remaining studies compared DSA-MRA against IADSA (11 patients with ICH; no false-positives or false-negatives),28 3-dimensional CT angiography against surgical findings (61 patients with massive, acute ICH requiring surgical decompression; sensitivity=55%, 95% CI, 38 to 71; specificity=97%, 95% CI, 83 to 99; positive predictive value=94%, 95% CI, 74 to 99; and negative predictive value=67%, 95% CI, 53 to 80),24 and “dynamic” CT angiography against IADSA (44 patients with spontaneous lobar ICH; sensitivity=88%, 95% CI, 69 to 96; specificity=95%, 95% CI, 76 to 99; positive predictive value=95%, 95% CI, 78 to 99; and negative predictive value=86%, 95% CI, 66 to 95).25

**Trinational Survey of Professional Organizations**

**Survey Response**

We sent 1410 questionnaires. There were 692 (49%) respondents, of whom 617 (44%) were involved in the investigation of patients with ICH (supplemental Figure IV, available online at http://stroke.ahajournals.org). The proportion of physicians who responded was higher for France than for the Netherlands or the United Kingdom (P<0.001). The proportion of responders differed among professional groups (P<0.001): 51% of stroke specialists (n=180), 46% of neurosurgeons (n=161), 44% of neuroradiologists (n=155), and 34% of neurologists (n=121). The completeness of the responses received was excellent (median completeness=99%; range, 89% to 100%).

**Survey Results**

**Extent of Investigation**

The proportion of respondents who decided to perform 1, 2, or 3 investigations varied considerably among the 8 cases (the Figure). For example, the case of the patient age 41 years with a lobar ICH and no prestroke hypertension attracted the greatest proportion of respondents who would investigate once, twice, or 3 times (99%, 87%, and 56%, respectively), whereas these proportions were lowest (31%, 6%, and 1%, respectively) for the case of the patient age 83 years with a deep ICH and prestroke hypertension. The strongest influence on the decision to investigate at all was younger patient age, followed by the absence of prestroke hypertension, and these influences remained but were weaker as the decision to further investigate was made (Table 2). There was no significant difference among countries in the proportion of physicians investigating once. The proportions of physicians investigating twice (P=0.001) or 3 times (P=0.03) differed among countries, with French physicians tending to investigate more (supplemental Figure V, available online at http://stroke.ahajournals.org). Differences were also observed among specialties (P<0.001): neurosurgeons less frequently requested investigations (supplemental Figure VI, available online at http://stroke.ahajournals.org). Despite the consistency in respondents’ decisions to investigate nonhypertensive, younger patients with lobar or deep ICH (97% to 99%), they were less consistent about a hypertensive younger patient with a deep ICH, whom 89% of respondents would investigate once and 57%, twice.
Type of Investigation
The radiological technique(s) used varied somewhat among the 8 cases (supplemental Table I, available online at http://stroke.ahajournals.org). The use of IADSA varied according to the characteristics of the patient, the location of the ICH, country, and specialty (supplemental Table II, available online at http://stroke.ahajournals.org). For example, in the nonhypertensive patient age 41 with lobar ICH (case 1), the proportion of respondents who did not perform IADSA at any stage was 27% overall, but this varied among countries (from 15% for France to 46% for the Netherlands) and specialists (from 41% for neurologists to 16% for neurosurgeons). Despite the general agreement about the need for investigation of a patient age <45 years without a history of hypertension and with lobar ICH (case 1, the Figure), there were 33 different approaches to the number, order, and types of investigation used.

Timing of Investigation
Most first- and second-line investigations were performed within the first 3 months of ICH onset. There was a tendency to perform these investigations within 1 to 2 days in younger patients, with little apparent influence of hypertension and ICH location (supplemental Table I).

Discussion
In a systematic review of studies describing radiological investigations of ICH, we found selection biases and small sample sizes. In studies of the yield of IADSA, roughly one third of patients had an AVM or aneurysm, with a lower yield in patients with a history of hypertension or a deeply located ICH but an appreciable yield in older patients. However, in a survey of current practice, younger patient age strongly influenced whether further investigation of ICH was performed, followed by the absence of prestroke hypertension and lobar ICH location, which is in line with existing recommendations.7-8 Nevertheless, the types and timing of investigations varied considerably among specialties and countries.

Our systematic review benefited from a thorough search strategy, but the paucity of relevant studies and their variable quality precluded meta-analysis and firm conclusions. Our survey had several strengths. There were 617 responses, and the survey encompassed the 4 pertinent groups of specialists and 3 countries. The response rate was ~50%, which is quite good for surveys. However, the survey’s global coverage was

Table 2. Univariable Associations Expressed as Odds Ratios (95% CIs) of Patient Characteristics With Respondents’ Inclination to Investigate ICH Once, Twice, or 3 Times

<table>
<thead>
<tr>
<th>No. of Times Investigated</th>
<th>Younger Age*</th>
<th>No History of Prestroke Hypertension</th>
<th>Lobar Hematoma Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Once</td>
<td>16 (13 to 20)</td>
<td>5 (4 to 6)</td>
<td>2 (1 to 2)</td>
</tr>
<tr>
<td>Twice</td>
<td>9 (7 to 10)</td>
<td>3 (2 to 3)</td>
<td>2 (1 to 2)</td>
</tr>
<tr>
<td>3 Times</td>
<td>10 (8 to 12)</td>
<td>2 (2 to 3)</td>
<td>2 (1 to 2)</td>
</tr>
</tbody>
</table>

*Younger patients (age 38, 39, 41, and 43 years) vs older patients (age 72, 75, 80, and 83 years).
limited by both logistical and resource constraints, so it has limited generalizability. To minimize the burden on respondents, we limited the survey to 8 cases, which inevitably curtailed our ability to explore the influence of patient age on investigation patterns and may have inflated the odds ratios in Table 2. Furthermore, the emphasis on radiological detection of structural abnormalities precluded an evaluation of the influence of radiological “surrogate markers” of small-vessel diseases (such as brain microbleeds, white matter hyperintensities, and lacunes). Since our literature search was conducted, several studies have described the diagnostic utility of CT angiography, compared with IADSA or surgical or pathological findings, and have confirmed that false-negatives and false-positives do occur with a frequency similar to those in the studies included in our systematic review.29–32

Because there have been few studies of the best diagnostic strategy for detection of a vascular malformation underlying ICH, firm recommendations for clinical practice are impossible.7,8 However, there is a risk of missing an underlying aneurysm or AVM in most patient and ICH subgroups if angiographic imaging is not performed (Table 1). Detection of an underlying AVM, aneurysm, dural arteriovenous fistula, or intracranial venous thrombosis is important because timely treatment can prevent recurrent ICH. Furthermore, delayed MRI may help identify an underlying tumor or cavernous malformation, Therefore, MRI and angiographic imaging seem worthwhile, depending on the patient’s clinical condition,3 but the availability and choice of these modalities will depend on local health care systems.

Despite the availability of a wide variety of imaging technologies for investigating ICH,2 the understanding of how to apply them in clinical practice is limited, resulting in variation among patients, countries, and specialties. Until further studies of the diagnostic accuracy of noninvasive investigations such as CT angiography or MRA have been performed, these techniques cannot replace IADSA for the investigation of ICH. Future research should also focus on the appropriate timing of investigation after ICH onset and the most parsimonious strategies for investigating patients at older ages and in resource-poor settings.

Acknowledgments

We are very grateful to Rosemary Anderson for administrative assistance, Aidan Hutchinson for programming expertise, the professional organizations who shared their mailing lists for this survey (supplemental Figure III), and the members of these organizations who responded to the survey.

Sources of Funding

C.C. was funded by EA2691 and ADRINORD, and R.A.–S.S. was funded by the UK Medical Research Council. J.v.B. was funded by the UK Medical Research Council. J.v.B. was funded by the Netherlands Organization for Scientific Research and the Netherlands Heart Foundation (grant No. 2002B138). C.J.M.K. was supported by a clinical fellowship from The Netherlands Organization for Health Research and Development (grant No. 907-00-103) and by a grant from the Netherlands Heart Association (grant No. 2007B1048).

Disclosures

None.

References


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*Stroke*. 2010;41:685-690; originally published online February 18, 2010;
doi: 10.1161/STRKEAHA.109.572495
*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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