Poststroke Memory Function in Nondemented Patients
A Systematic Review on Frequency and Neuroimaging Correlates

Liselore Snaphaan, MSc; Frank-Erik de Leeuw, MD

Background and Purpose—Poststroke memory dysfunction is a prerequisite for the diagnosis of poststroke dementia. This diagnosis is made within months after a stroke, apparently assuming a relatively stable course of the poststroke memory function. Clinical experience added to anecdotal evidence from the literature suggests that poststroke memory function may be reversible. The aim of the present study was to systematically review the available data on the time course of poststroke memory function in nondemented stroke survivors. In addition, we wanted to investigate the role of (pre-)stroke characteristics on poststroke memory function.

Methods—We performed systematic literature search of PubMed with the following medical subject heading terms: memory and stroke. The search strategy yielded 798 articles of which 65 fulfilled our inclusion criteria and went on to the data extraction stage.

Results—Five studies reported the prevalence of poststroke memory dysfunction at different poststroke intervals. The prevalence of poststroke memory dysfunction varied from 23% to 55% 3 months poststroke, which declined from 11% to 31% 1 year poststroke. Larger stroke volume, prestroke medial temporal lobe atrophy, and white matter lesions were related with decreased poststroke memory function.

Conclusions—Not all patients with poststroke memory dysfunction 3 months after a stroke had memory dysfunction 1 year poststroke. Consequently, not all criteria for the dementia diagnosis were fulfilled any more. This may indicate that poststroke dementia may be reversible in a substantial proportion of patients with stroke. Preferably, standardized reassessment of cognitive function should be performed in each patient diagnosed with poststroke dementia. (Stroke. 2007;38:198-203.)

Key Words: cognitive ■ prevalence ■ stroke

Poststroke memory dysfunction (PMD) is, by definition, a prerequisite for the diagnosis of poststroke dementia (PSD) or vascular dementia (VaD), albeit not a prominent clinical feature of the poststroke cognitive profile. This diagnosis is made within months after a stroke, apparently assuming a relatively stable course of PMD. This is in contrast to what is common in clinical practice, because the prevalence of PMD is known to vary from 50% within the first few weeks after a stroke gradually decreasing to 12% 6 months after a stroke. The presence of PMD is required to fulfill clinical diagnostic criteria for dementia. This may suggest that poststroke dementia may be reversible in a substantial proportion of patients with stroke that initially have been diagnosed with PSD.

Surprisingly, formal studies investigating the time course of poststroke memory function (PMF) are scarce. This may allow for potential misclassification of poststroke dementia or VaD when memory function changes over time (the presence of memory dysfunction is a symptom needed to fulfill this clinical diagnosis).

Another reason for investigating the true occurrence of PMD is that a stroke only seldom occurs in the brain structure that is predominantly involved in memory encoding and retrieval (the medial temporal lobe). Despite this, the frequency of PSD or VaD is estimated to be over 30%, which may suggest that other (pre-)stroke characteristics are related to PMF such as white matter lesions (WML), medial temporal lobe atrophy (MTA), previous (silent) infarcts, and prestroke cognitive function. Many studies have investigated the epidemiology of PMF. However, some methodological limitations must be considered, including small sample size, inability to adjust for confounding factors, and unclear operationalization and description of the timing of assessment of memory function. Only a few addressed the role of stroke characteristics and that of the previously mentioned presumed prestroke characteristics in patients with PMD. It is important to know the course of PMF, because albeit the preeminent factor in the PSD and VaD diagnosis, it may not even be present (to the same extent) over 3 months after the stroke as it was during the diagnosis of PSD and VaD (within 3 months after stroke).
We systematically reviewed the available data on frequency, time course, and risk factors of poststroke memory function in nondemented stroke survivors. Second, we evaluated the effect of location and severity of stroke on PMF. In addition, we wanted to investigate the role of prestroke structural brain changes, including WML, MTA, previous (silent) infarcts, and prestroke cognitive decline, on the frequency of PMF.

Methods
A literature search of the electronic database PubMed was performed from March to May 2006. We entered the following medical subject heading terms and text words in full and truncated: memory and stroke. In accordance with the literature, the term stroke includes both cerebral infarcts and intracerebral hemorrhages. The search was limited to the English language and included human studies with participants of 45 years of age or over. We followed a two-step approach in this selection of eligible articles (see Figure). First, one reviewer (L.S.) screened the abstracts for the following characteristics: (1) original article published in English on case–control or cohort studies (sample size had to be at least 15), and (2) information about memory and stroke had to be present. From screen-positive abstracts, full articles were collected that then went to a second selection step to identify articles that fulfilled the following inclusion criteria: (3) description and operationalization of poststroke memory function; (4) description of the stroke (at least one of the following characteristics had to be present: location, severity, and first-ever stroke); (5) description of presumed prestroke factors that could possibly influence poststroke memory (WML, previous stroke, MTA, and prestroke cognitive function). Papers were evaluated against the inclusion criteria by two authors independent from each other (L.S. and F.E.d.L.); in case of disagreement, a consensus meeting was held.

Results
The search strategy yielded 798 articles. After screening of the title and the abstracts, 101 articles were retrieved full-text and examined against the inclusion and exclusion criteria, of which 65 were included and went on to the data extraction stage (Figure).

Time Course of Poststroke Memory Function
The most common tests that were used to assess verbal memory function were the Wechsler Memory Scale,10 the Rey Auditory Verbal Learning Test,11 the Rivermead Behavioral Memory Test,12 the Cambridge Assessment Of Mental Disorders,13 the California Verbal Learning Test,14 and the Verbal Learning Task.15

Five studies5,16–19 investigated the formal time course of poststroke memory dysfunction that had all included patients with first-ever stroke at different poststroke intervals (Table 1). There was a general tendency of a reduced (verbal) memory function (Table 2) among stroke survivors as compared with controls (healthy controls or normative data).

There were 10 studies that attempted to operationalize PMD, each with their own defined cutoffs (see details in Table 1).4,5,16–19,35–38

The prevalence of PMD ranged from 50% weeks after the stroke to 11% more than 1 year after the stroke (for details, see Table 1).

Relation Between Poststroke Memory Function and Stroke Characteristics
Table 2 presents an overview of poststroke memory function (assessed at different stroke–memory assessment intervals) in relation to possible (pre-)stroke confounding factors.

Several studies provided a clear description of the size (volume)26,39–43 and the location4,16,25,33,34,42–51 of the infarction; however, the relation with PMF was only seldom investigated. In one study,42 a linear relation between the size of the infarction and the degree of PMF was found. More circumstantial evidence for a role of stroke severity with respect to PMF comes from a study41 that found a larger total volume of infarction among those patients who developed poststroke dementia.

Cerebral infarcts in the left middle temporal gyrus and the and/or left dorsal lateral frontal cortex were significantly correlated with PMF.36 Four studies33,38,44,48 found a lower PMF in left-sided stroke compared with right hemispheric stroke. Most studies found left hemispheric stroke to be related to more severe PMD as compared with the right hemisphere, presumably because most memory tasks rely on intact language function, although these studies also included nonverbal memory tasks.

Relation Between Prestroke Characteristics and Poststroke Memory Function
There are a number of factors that presumably were already present before the stroke (including WML,52–54 MTA55,56
TABLE 1. Prevalence of Poststroke Memory Dysfunction: A Time Course

<table>
<thead>
<tr>
<th>Stroke Survivors</th>
<th>Prevalence of Poststroke Memory Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>Mean Age, y (SD)</td>
</tr>
<tr>
<td>-----</td>
<td>------------------</td>
</tr>
<tr>
<td>4</td>
<td>16</td>
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<tr>
<td>37</td>
<td>78</td>
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<tr>
<td>38</td>
<td>220</td>
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<tr>
<td>35</td>
<td>30</td>
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<tr>
<td>36</td>
<td>229</td>
</tr>
</tbody>
</table>

Note: Empty cells indicate no assessment. NS indicates not specified; Y, yes; AVLT, Auditory Verbal Learning Test; RBMT, Rivermead Behavioural Memory Test; WMS, Wechsler Memory Scale.

Previous [silent] infarcts, and prestroke cognitive decline that could be related to PMF. As a result of the fact that stroke patients usually did not have neuroimaging and/or neuropsychology before the actual stroke, the effects of these factors on PMD are difficult to disentangle from the direct stroke effects. Some studies tried to overcome this problem by making adjustments for WML and MTA.

White Matter Lesions

WML was scored in only five of 12 studies. Their presence, as assessed by means of semiquantitative rating scales, varied from 15% to 45%. In general, there was a lower PMF among patients with WML compared with those without otherwise identical demographic and stroke characteristics. WML were associated with global cognitive impairment in patients with stroke. Independent of this finding, there was a significant association between left frontal WMH volume and poststroke working memory and between both left and right temporal WMH volumes and memory function (not otherwise specified).

Medial Temporal Lobe Atrophy

The degree of MTA was assessed in only two studies. Their presence (as assessed on a semiquantitative scale) was strongly related to immediate and delayed poststroke memory function (not otherwise specified) among 260 stroke survivors. This is in line with findings among 22 stroke survivors in which there was a relation between poststroke verbal memory as assessed with the Verbal Learning Task and prestroke MTA.

Preceding (silent) Infarcts

Information on previous (silent) infarction was lacking in most studies. Twenty-one articles included first-ever stroke survivors and 44 articles included also patients with multiple strokes or did not specify this. One article related silent stroke to memory. They found that silent infarctions located in the thalamus were associated with a greater decline in memory performance (z-score = −0.50; 95% CI, −0.87 to −0.13).

Prestroke Cognition

None of the 65 included articles investigated prestroke cognition in relation to poststroke memory function.

Discussion

Data from 65 studies were reviewed. The prevalence of poststroke memory dysfunction in nondemented stroke survivors varied from 13% to 50% weeks after the stroke, which declined to 11% to 31% 1 year (or more) after the stroke (Table 1). It could be that poststroke dementia is reversible in some patients with stroke that have initially been diagnosed with PSD. Preferably, standardized reassessment of cognitive function should be performed in each patient diagnosed with PSD. Unfortunately, this is not part of current diagnostic criteria (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition or NINDS-AIREN). A prerequisite for the description of a reliable time course of PMD is the presence of a stable source population and a complete as possible follow up; otherwise, the prevalence may appear to decrease when cases (those with PMD) selectively die.

However, some methodological aspects must be considered. The measurement of PMD at several poststroke intervals was assessed in five studies. Therefore, the ascertainment of a time course of PMD prevalence relies on different studies that investigated PMD at different poststroke intervals. However, these studies differed tremendously in terms of patient inclusion, assessment of

...
memory function, and in the collection of stroke and prestroke (imaging) characteristics.

In addition, and not always explicitly mentioned, most studies included patients who were able to complete neuropsychologic examination. As a consequence, patients who could not complete testing (with a presumably larger stroke than those who could be examined) and those with aphasia were not examined. This could have led to an underestimation of PMD. On the other hand, people with only a minor stroke may not have been included because they, for example, were not willing to participate months after a stroke from which they had completely recovered already.

Some studies investigated patients derived from a larger cohort (also includes one population-based study) that apparently had manifestations of cerebral ischemia, either on a scan (in that case, it was unclear whether the infarct had been symptomatic or not) or based on history-taking. These results are most likely not to be compared with patients with “recent” stroke because it seems likely that both stroke characteristics and memory function differ between early stroke survivors and “ever stroke” patients.

Another source of bias that may lead to underestimation of PMD is the fact that all studies only included patients that were actually admitted to the hospital. Many patients with stroke,
especially the most severely affected with presumably prestroke cognitive impairment or even dementia, are not admitted to the hospital. It seems likely that they are the ones with the highest prevalence of PMD and the highest risk of PSD. Some studies excluded patients who appeared demented immediately after stroke. Consequently, the remaining sample (that then does not encompass any demented patient) has a lower risk of developing PSD.

We found a considerable age difference between the studies making comparisons difficult, because age is an important determinant of memory. In addition, age is an important determinant of both MTA and WML, the latter being one of the most important confounders or effect modifiers in the relation between stroke and PMD. The possibility that differences in MTA or WML underlie (at least in part) the observed differences of PMD between studies can therefore not be ruled out.

There was a wide variability in assessment of verbal memory function and the definition of memory dysfunction. From most studies, the memory dysfunction (for example, expressed as the number SDs below the mean) could not be calculated as a result of lack of raw data. Therefore, the prevalence of PMD across different poststroke intervals is rather limited and difficult to compare. Other studies used normative data or controls to define memory function. However, the problem with normative data could be that there is not much known about the persons investigated and they certainly did not undergo neuroimaging. Therefore, normative data could also include people with a silent stroke or WML.

The mentioned methodological considerations may lead to questioning the validity of the concept of PMD and consequently of the diagnosis of VaD and PSD. These diagnoses are based (analogous to the diagnosis of Alzheimer disease) on the assumption of a stable or gradual decline of poststroke memory function among patients without prestroke characteristics that could be related to PMD. Our review indicates that this is not true. Patients with PMD 3 months after a stroke (who could then have been diagnosed with VaD or PSD when also all other dementia criteria were fulfilled) could very well have recovery of memory dysfunction 6 months after the stroke and consequently not fulfill dementia diagnosis any more. We also found that patients with PMD appear to constitute a population with many other (pre-)stroke factors that could, independent from the stroke, be related to PMD, both structural as well cognitive.

The development of PMD also seems counterintuitive, because the stroke does usually not affect structures known to be involved in memory. However, the emergence of poststroke memory dysfunction fits in current thinking of memory as a function of an intact cerebral network, connecting several parts of the brain, including medial temporal lobes, anterior thalamic nucleus, mammillary body, fornix, and the prefrontal cortex with each other (the so-called circuit of Papez). Any stroke in either of these structures or in the connections in between could result in PMF. Presumably, patients with already preexisting damage in either compartments of the network (MTA) or in the connections (WML) are at increased risk for PMD. Perhaps these are also the patients who are therefore at the highest risk for PSD, although formal studies are lacking. Therefore, future studies should include well-characterized patients with stroke (both in terms of stroke and prestroke characteristics) that assess memory function at several predefined poststroke intervals. They should particularly include information on whether ever or first-ever stroke survivors are included because a previous stroke may influence cognitive function assessed immediately after another, novel stroke. Care should be given to proper registration of those patients who cannot complete memory testing. Novel imaging techniques such as task-related, but also resting state functional magnetic resonance imaging, may be of use in the detection of what part of the brain (or what network) shows altered function in patients with PMD. These techniques could then, when established, perhaps also be of use in the early prediction of those with PMD or even poststroke dementia and as such possibly guide early (cognitive) rehabilitation medicine.

Disclosures
None.

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