Silent and Symptomatic Infarcts on Cranial Computerized Tomography in Relation to Dementia and Mortality

A Population-Based Study in 85-Year-Old Subjects

Martin Liebetrau, MD; Bertil Steen, MD, PhD; Gerhard F. Hamann, MD; Ingmar Skoog, MD, PhD

Background and Purpose—Incidental findings of infarcts on brain imaging are common, but their clinical significance is not clear. We examined the prevalence of symptomatic and silent infarcts on cranial computerized tomography (cCT) and their relation to dementia and mortality in a representative sample of 239 85-year-olds living in Gothenburg Sweden.

Methods—Information on stroke was obtained from an inpatient hospital linkage system, self-reports, and key informants. Dementia was defined according to the Diagnostic and Statistical Manual of Mental Disorders, 3rd revision. Cortical and lacunar infarcts were diagnosed on cCT.

Results—The prevalence of cerebral infaracts was 17.1%, and half of those were clinically silent (8.6%). The frequency of dementia was increased in those with symptomatic (OR, 5.5; 95% CI, 2.1 to 14.1) and silent infarcts (OR, 2.7; 95% CI, 1.1 to 6.7). Infarcts increased the risk for dementia and its severity in women but not in men. The 3-year mortality rate was increased in those with symptomatic (OR, 4.0; 95% CI, 1.6 to 9.6) and silent infarcts (OR, 3.4; 95% CI, 1.4 to 8.5).

Conclusions—Almost one fifth of 85-year-olds have infarcts on cCT, and half of those are clinically silent. These infarcts are related to an increased rate of dementia and 3-year mortality. Cerebrovascular disease as a cause of dementia may be underrated because of silent infarcts. It has to be elucidated whether treatment of risk factors for stroke may reduce the consequences of silent infarcts. (Stroke. 2004;35:1816-1820.)

Key Words: infarcts, silent ■ dementia ■ elderly ■ epidemiology ■ mortality

The frequency of dementia and stroke increases with age. These disorders have become major health problems in Western societies because of the increasing number of elderly people. Many strokes are clinically silent, and their frequency is reported to increase with age. Silent brain infarcts were previously regarded to be of little clinical significance but have recently been reported to be related to an increased incidence of future stroke and dementia.

The frequency of clinically silent infarcts might be overestimated in elderly populations, because elderly individuals may not remember a stroke because of cognitive impairment or they may not be admitted to hospital for their stroke. We have recently reported on the importance to use several different sources of information to obtain a stroke history in the elderly.

Most studies on silent infarcts have been performed on magnetic resonance imaging (MRI), which has several advantages over cranial computerized tomography (cCT) scan, such as a higher sensitivity to detect small infarcts. However, cCT is still widely used in Western countries and will be the main imaging tool in the developing world for the next decades. Findings regarding cCT therefore still have clinical implications.

The aim of this study was to estimate the prevalence of symptomatic and silent infarcts on cCT and its relation to dementia and mortality in a population-based study of 85-year-olds.

Subjects and Methods

All 85-year-olds born between July 1, 1901, and June 30, 1902, and registered for census purposes in Gothenburg, Sweden were invited to take part in a health survey. The sample has been described in detail previously and included 494 individuals (response rate 64%; 347 nondemented and 147 demented), and it was found to be representative for all 85-year-olds in Gothenburg.

All demented (n=147) and a systematic subsample of 269 nondemented individuals were invited to cCT; 104 demented (response rate 70.1%; 28 men, 76 women) and 135 nondemented (response rate 50.2%; 46 men, 89 women) individuals accepted (n=239). There were no significant differences between participants and nonparticipants within the demented and nondemented groups regarding gender, marital status, registration as a psychiatric outpatient or inpatient, mental disorders, institutionalization, 3-year mortality rate, history of focal neurological symptoms, cardiovascular disorders, hypertension, or mean systolic and diastolic blood pressure.

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From the Department of Neurology (M.L., G.F.H.), Klinikum Grosshadern, Ludwig-Maximilians-University, Munich, Germany; the Department of Geriatric Medicine (B.S.) and the Institute of Clinical Neuroscience (M.L., I.S.), Neuroepidemiology Unit, Sahlgrenska Academy, Göteborg University, Göteborg, Sweden.

Correspondence to Dr Ingmar Skoog, Institute of Clinical Neuroscience, Department of Psychiatry, Sahlgrenska University Hospital, SE-41345 Göteborg, Sweden. E-mail ingmar.skooog@neuro.gu.se

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Thirty-nine men and 115 women had ≤6 years of education, and 24 men and 32 women had more education than that (missing information in 25 demented and 4 nondemented individuals).

Informed consent was obtained from all participants or their relatives. The study was approved by the Ethics Committee for Medical Research at Göteborg University in Gothenburg.

The study included nurse home visits, physical examinations by geriatricians, neuropsychiatric examinations, key informant interviews and laboratory tests as described previously.⁶

CT Scan Examinations
All cCT scans were performed without contrast enhancement and with 10-mm continuous slices on a Philips Tomoscan 310 (n = 133) and a General Electric 8800 (n = 106). The median interval between the psychiatric examination and CT scan was 13 days, the mean time was 27.0 (SD ± 42.6) days. The cCT scans were examined for ischemic infarcts (large cortical infarcts and lacunar infarcts) and white matter lesions (WML) by 2 experienced radiologists, blinded to the results of the other examinations.

Diagnostic Procedures

Stroke
Information on stroke/transient ischemic attack (TIA) was derived from 3 different sources of information: a hospital linkage system, self-reports, and key informants.⁶ All individuals (n = 239) and 198 close informants were interviewed by a neuropsychiatrist regarding the occurrence of stroke. The participants were also interviewed by a geriatrician who examined the participants regarding focal signs indicating previous stroke/TIA. All side notes and answers to these questions were examined by a neuropsychiatrist and a stroke neurologist. Only patients with a definite history of acute focal symptoms (eg, hemiparesis or acute aphasia) were included. The computerized inpatient register system includes all individuals who were admitted to hospital with a main or secondary diagnosis of stroke/TIA since 1978 according to the International Classification of Diseases, 9th edition (ICD-9) (ICD-9 codes 430 to 438 for stroke/TIA). According to previous studies, 94% of registered strokes are correctly classified.⁸

We used a conservative approach for the definition of silent infarcts, which were defined as individuals with infarcts on cCT without any history of stroke/TIA irrespective of whether the stroke symptoms corresponded to the lesion. Symptomatic infarcts were defined as individuals with infarcts on cCT and a history of stroke/TIA.

Dementia
The diagnosis of dementia was made according to the Diagnostic and Statistical Manual of Mental Disorders, 3rd revision (DSM-III-R)⁷ as previously described.⁷ Severity of dementia was also diagnosed according to the DSM-III-R criteria, in which the degree of severity is related to the need for assistance in daily living.

Statistical Methods
The association between infarcts on cCT, history of stroke, dementia, and 3-year mortality were tested for significance with Fisher exact test, odds ratios were calculated with logistic regression analyses. Confidence intervals (at the 95% level) were calculated with exact tests using binomial distribution. Correction for oversampling of dementia was performed by first calculating the prevalence of infarcts in nondemented and demented individuals separately and then calculating the total prevalence of infarcts in the population by using the known prevalence of dementia in the population as reported previously.⁷ We also included education in logistic regression analyses, but this did not change the odds ratios considerably. Because of the large group of demented subjects with no information on education, we chose not to show these analyses.

Table 1 shows the baseline characteristics in demented and nondemented individuals. The demented subjects had less hypertension and a higher 3-year mortality rate.

Results

Prevalence of Cerebral Infarcts on cCT
The prevalence of cerebral infarcts was 19.2% (46/239), with no gender difference. After correction for oversampling of demented individuals in the general population, the prevalence of infarcts was 17.1%. Among the 46 individuals with infarcts on cCT, 16 (34.8%) had only large infarcts, 29 (63.0%) had only lacunar infarcts, and 1 (2.2%) had both.

Infarcts on cCT in Relation to History of Stroke
Among those with infarcts on cCT, 47.8% had no history of stroke/TIA from any of the 3 different sources of information. The prevalence of silent infarcts was thus 9.2% (men 8.1%, women 9.6%). After correction for oversampling of dementia, the prevalence of silent infarcts was 8.6%.

If only 1 source of information was used to exclude history of stroke/TIA, the prevalence of silent infarcts was higher than using all 3 sources (Table 2). The proportion of lacunar infarcts was higher among those with silent infarcts than in those with symptomatic infarcts (77.3% versus 52.2%; OR, 3.1; 95% CI, 0.9 to 11.3).

Among those with a of stroke history (n = 64), infarcts on CT were found in only 24 cases (38%). For the different sources of information, an infarct was found in 30% (14/46)

<p>| TABLE 2. Prevalence and Proportion of Silent Infarcts Depending on Different Sources of Information |</p>
<table>
<thead>
<tr>
<th>Source of Information to Detect Stroke History (Infarcts on cCT/Individuals With This Source of Information)</th>
<th>Proportion of Silent Infarcts/Total Infarcts, n (%), 95% CI</th>
<th>Silent Infarcts in the Total Population %, (Corrected)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-reports (n = 46/239)</td>
<td>32 (69.6, 54.1–81.8)</td>
<td>13.4 (12.7)</td>
</tr>
<tr>
<td>Relatives (n = 38/198)</td>
<td>20 (52.6, 36.1–68.7)</td>
<td>10.1 (8.8)</td>
</tr>
<tr>
<td>Self-reports and relatives (n = 46/239)</td>
<td>25 (54.3, 39.1–68.8)</td>
<td>10.5 (10.0)</td>
</tr>
<tr>
<td>Hospital linkage system (n = 46/239)</td>
<td>28 (60.9, 45.4–74.6)</td>
<td>11.7 (10.8)</td>
</tr>
<tr>
<td>All information (n = 46/239)</td>
<td>22 (47.8, 33.1–62.9)</td>
<td>9.2 (8.6)</td>
</tr>
</tbody>
</table>
of self-reported strokes, in 47% (18/38) of those reported by key informants, and in 39% (18/46) of those found in the hospital linkage system. In the latter source, 10.9% were recorded as TIA. No major differences were observed when demented and nondemented individuals were analyzed separately. Either a history of stroke or an infarct on cCT was found in 86 (36.0%) of the 85-year-olds (31.4% after correction for oversampling of dementia).

Cerebral Infarcts in Relation to Dementia
The prevalence of dementia was higher in individuals with infarcts on cCT than in those without (63.0% versus 38.9%; OR, 2.7; 95% CI, 1.4 to 5.2). Individuals with silent infarcts on cCT had almost 3-fold increased odds of dementia than 85-year-olds without history of stroke or infarcts on cCT (Table 3). The odds of dementia were even more increased in those with history of stroke without infarcts on cCT, and in those with infarcts on cCT and history of stroke. Silent infarcts were related to dementia irrespective of source of information used to exclude stroke.

The frequency of WMLs was higher in subjects with infarcts on cCT than in those without (63.0% versus 38.9%; OR, 2.7; 95% CI, 1.4 to 5.2). Compared with those without WMLs, stroke history, or infarcts, the odds ratio for dementia in those with WMLs without stroke or infarcts was 4.3 (95% CI, 2.1 to 9.0), in WMLs with silent infarcts 9.3 (95% CI, 2.8 to 30.8), in WMLs with history without infarct 19.7 (95% CI, 5.8 to 66.3), and in WMLs with symptomatic infarcts 15.0 (95% CI, 4.3 to 52.2).

The dementia was more severe in those with infarcts on cCT (mild dementia 10.3%, moderate dementia: 31.7%, severe dementia 58.6%) than in those without infarcts on cCT (mild 32.0%, moderate 37.3%, severe 30.7%; test of linear-by-linear trend P=0.004).

Women showed a trend for a higher prevalence of dementia than men among individuals with infarcts on cCT (82.8% versus 58.8%; OR, 3.4; 95% CI, 0.9 to 13.1). The odds for dementia were higher in women than in men among those with lacunar infarcts (OR, 4.9; 95% CI, 1.0 to 24.2), whereas no such difference was found among those without infarcts (OR, 1.2; 95% CI, 0.7 to 2.2). The dementia was more severe in women than in men with infarcts on cCT (OR for severe dementia in women compared with men, 11.2; 95% CI, 1.2 to 105.1), whereas no such sex difference was found among those without infarcts on cCT (OR, 0.8; 95% CI, 0.3 to 1.9).

Three-Year Mortality Rate in Those With Cerebral Infarcts
Overall, the 3-year mortality rate was higher in those with than in those without infarcts on cCT (OR, 2.7; 95% CI, 1.4 to 5.2). Mortality rate was increased in those with silent infarcts, symptomatic infarcts, and stroke history without infarcts compared with those without infarcts or stroke history (Table 4).

Discussion
Almost one fifth of 85-year-olds had infarcts on cCT. Half of those were silent despite using 3 sources of information (self-reports, key-informants, and hospital linkage system) to exclude history of stroke. Silent infarcts had clinical relevance, because they were associated with increased odds of dementia and 3-year mortality. This adds to recent studies showing that silent infarcts are related to an increased incidence of future stroke and dementia. Furthermore,
Cerebral infarcts on cCT or stroke history (elucidated by 3 sources of information) were found in more than one third of this population of 85-year-olds, further underlining the importance of cerebrovascular disease in the very elderly.

Almost one tenth of 85-year-olds had silent infarcts on cCT. Two other population studies examined the frequency of silent infarcts on MRI and reported even higher frequencies\(^{10,11}\) of 35% in individuals \(\approx 85\) years old.\(^{10}\) However, none of those studies combined self-reports, relatives, and a hospital linkage system to detect stroke history. In our study, the proportion of silent infarcts among all infarcts (48%) decreased the more sources of information that were used. Using only self-reports, 70% of all infarcts detected by cCT were silent, which decreased to 54% when information from key informants was added. A second reason for the low frequency was that we used a conservative approach for the definition of silent infarcts, which were defined as individuals with infarcts on cCT without any history of stroke or TIA, irrespective of whether the symptoms corresponded to the lesion. Thus, in some cases of symptomatic stroke, the infarct might have been at a different location than indicated by the clinical symptoms. However, individuals often have difficulties remembering having a stroke and thus even more difficulties remembering details of the symptomatology. Therefore, classification of silent infarcts in individuals with a history of stroke is uncertain. Finally, probably even more important, the other studies used MRI whereas we used cCT, which has a lower sensitivity than MRI to detect small cerebral infarcts.\(^{2,12,13}\) This is supported by the Rotterdam study, in which the proportion of large infarcts (10%) among the silent infarcts was lower than in our study.\(^{2}\) However, lesions detected by cCT may have more clinical consequences.\(^{12}\)

A large proportion of those with a stroke history had no infarcts on cCT. One reason for this might be the use of cCT, which may not detect small infarcts in the brain stem or cortex. Another reason might be that it was difficult to separate TIA and stroke by self-report and key informants. However, the frequency of TIA in those admitted to hospital for stroke reasons was only 11%. It is noteworthy that strokes reported by key informants was most often confirmed by cCT (in 47%), and that only 39% of patients with strokes diagnosed by the hospital stroke register had infarcts on cCT. Nevertheless, stroke history without infarcts on cCT was related to dementia and an increased mortality rate.

We found that silent and symptomatic infarcts, as well as stroke history without infarcts, were all related to dementia. This is in accordance with other studies reporting associations between infarcts on cCT scan\(^{14}\) or MRI\(^{15}\) and dementia. The relation between silent infarcts and dementia has been debated.\(^{16}\) However, empirical evidence is scarce. Only one population study has previously reported on the association between silent infarcts and dementia, which found that silent infarcts at baseline increased the risk of dementia during follow-up.\(^{3}\) However, it was not clear whether people with symptomatic stroke during follow-up were excluded. Two studies reported that silent infarcts did not increase dementia risk in stroke patients.\(^{17,18}\) These results may be confounded by the effect of symptomatic infarcts. We excluded all cases of TIA or stroke from the silent infarct group, even if the symptoms could not be explained by the location of the infarct. Thus, the association with dementia reported in our study could not be explained by a history of stroke at other locations than the infarct. WMLs were more common in 85-year-olds with infarcts than in those without, and there was an interaction effect between WMLs and silent infarcts to increase the odds for dementia.

The association between infarcts on cCT and dementia was stronger in women than in men, especially regarding lacunar infarcts. Women with infarcts also had more severe dementia. There are several possible explanations for this gender difference. One is that fewer men survive to older ages. Survival effects are thus probably more pronounced in men. Thus, men in this age group may be more resistant to factors causing dementia, or women may have vulnerability factors that increase their risk for dementia when cerebral insults occur. The findings are concordant with other studies reporting that the incidence of dementia is higher in women than in men after age 85.\(^{19,20}\)

Silent infarcts were related to an increased 3-year mortality rate, in accordance with 1 previous study in which silent infarcts increased mortality rate in individuals with clinical stroke.\(^{21}\) Our study is the first population-based study examining the mortality rate in stroke-free individuals with silent infarcts. The 3-year mortality rate in those with silent infarcts was in the same range as in individuals with symptomatic infarcts.

Some further methodological issues have to be discussed. Among the strengths of the study are the extensive data-gathering, that the sample was representative of the general population in this age group, and that it included individuals living in the community as well as those living in institutions.\(^{7}\) There are also some limitations. First, although there were no differences between participants and nonparticipants in the cCT-examined sample, the high refusal rate in the nondemented group necessitates that the question of representativeness be considered cautiously, because we cannot exclude the possibility that those who did not participate differed from participants in other factors. Second, we used cCT to detect infarcts. MRI obviously has several advantages over cCT in detecting infarcts, including a higher sensitivity to detect small infarcts. However, cCT is still widely used in clinical settings in Western countries and will likely be the main imaging tool in developing countries for the next decades. Our findings of an association between silent infarcts on cCT and dementia therefore have clinical implications. Third, the study was cross-sectional, which may limit the possibility to evaluate directions of associations. However, the cross-sectional design highlights the occurrence of silent infarcts in individuals with manifest dementia.

In summary, silent infarcts on cCT are common among the very elderly. Cerebrovascular causes of dementia may thus be underrated in epidemiological studies not using brain imaging. These silent infarcts have clinical consequences, such as increased risk for dementia, future stroke, and 3-year mortality rate. Thus, when silent infarcts are detected on brain imaging, a search for treatable risk factors should be exe-
cuted. It has to be elucidated whether treatment of risk factors for stroke may reduce the consequences of silent infarcts.

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