Silent brain infarcts and leukoaraiosis in young patients with first-ever ischemic stroke

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Tutkimuksen suorituspaikka: HY, neurotieteiden laitos
We investigated the features of and risk factors for magnetic resonance imaging (MRI)-
defined SBIs and leukoaraiosis in 1008 consecutive adults aged 15-49 years with first-
ever ischemic stroke. We analyzed the radiologic features of SBIs and leukoaraiosis in
MR-scanned patients (n=669) and examined their relation with subtype of the overt
stroke.

Of the 669 patients included, 13% had SBIs, 7% leukoaraiosis, 3% had both, and 550
free of these served as controls. Most of SBIs were located in basal ganglia (39%) or
subcortical regions (21%), but cerebellar SBIs were also rather frequent (15%).
Leukoaraiosis was mainly mild to moderate. Risk factors for SBIs were type 1 diabetes,
obesity, smoking, and increasing age. Risk factors for leukoaraiosis were type 1
diabetes, obesity, female sex, and increasing age. Small-vessel disease was the
predominant cause of stroke in both groups. Thus SBIs and leukoaraiosis are not
uncommon among young stroke patients-type 1 diabetes being the strongest risk
factor.

(151 words)
## Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Introduction</td>
<td>1</td>
</tr>
<tr>
<td>2 Literature review</td>
<td>3</td>
</tr>
<tr>
<td>2.1 Silent brain infarcts (SBI)</td>
<td>3</td>
</tr>
<tr>
<td>2.2 Leukoaraiosis (LA)</td>
<td>7</td>
</tr>
<tr>
<td>3 Patients and methods</td>
<td>11</td>
</tr>
<tr>
<td>4 Results</td>
<td>16</td>
</tr>
<tr>
<td>5 Discussion</td>
<td>20</td>
</tr>
<tr>
<td>6 Conclusions</td>
<td>24</td>
</tr>
<tr>
<td>7 References</td>
<td>25</td>
</tr>
</tbody>
</table>
Abbreviations

ADCav  average apparent diffusion coefficient
BMI    body mass index
CADASIL cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
CI     confidence interval
CT     computer tomography
DWI    diffusion-weighted MRI
FLAIR  fluid attenuated inversion recovery images
GM     subcortical gray matter
HI     hyperintensities over other white matter regions
LA     leukoaraiosis
LVD    cerebral large vessel disease
MR     magnetic resonance
OR     odds ratio
PANCS  primary angiitis of the CNS
PVH    periventricular hyperintensity
SBI    silent brain infarct
SLE    systemic lupus erythematosus
TOAST  Trial of ORG 10172 in Acute Stroke Treatment
WM     cerebral white matter
WMC    cerebral white matter changes
1 Introduction

A disturbance in the blood vessels supplying blood to the brain can cause rapidly developing loss of brain functions which is called a stroke. This can be due to ischemia (lack of blood supply) caused by thrombosis or embolism or due to a hemorrhage. By the definition of WHO, stroke has to persist beyond 24 hours or to be interrupted by death within 24 hours. When stroke-like symptoms last under 24 hours it is called TIA (transient ischemic attack). Stroke is the most common cause of death in USA and Europe (1) after heart infarct and cancer and additionally the most common cause of invalidity in the general adult population. Worldwide it is the second common cause of death. (2) The leading causes of death worldwide in 1990 were ischemic heart disease (6.3 million deaths), cerebrovascular accidents (4.4 million deaths), lower respiratory infections (4.3 million), diarrhoeal diseases (2.9 million), perinatal disorders (2.4 million), chronic obstructive pulmonary disease (2.2 million), tuberculosis (2.0 million), measles (1.1 million), road-trafﬁc accidents (1.0 million), and lung cancer (0.9 million). (2) Considerable amount of strokes occurs in population under 50 years old who are at the best age and still involved in the working life. (3) Thus strokes lead to early death, disabilities, invalidity and decreased employability.

The risk factors and etiology of strokes that occur in the young population differ signiﬁcantly from strokes that take place among the elderly people. (4) The stroke rate in Finland has been calculated to be 270-304 per 100,000 per year between 1974 and 1992. During past decades the incidence of stroke in Scandinavia and in western countries in general has decreased and it is expected to decrease also in the future. A Swedish population-based epidemiological survey among young adults aged 18 to 44 years in Northern Sweden observed in 1997 that the average annual incidence rate for ischemic stroke was 11.3/100 000 per year. (5) Furthermore, in Norway the average annual incidence among people aged 15 to 49 years with first-ever cerebral infarction in 1988-1997 was 11.4/100 000 per year. (6) Among the 1008 consecutive ischemic stroke patients aged 15 to 49 admitted to Helsinki University Central Hospital in 1994 to 2007, estimated annual occurrence of ischemic stroke was 10.8/100 000 (range 8.4 to 13.0), increasing exponentially with aging. (4) Treatment of stroke patients is most expensive
compared to other arteriolar illnesses. Thus it is important to recognize the risk factors to be able to do aggressive primary and secondary prevention.

However, overt symptomatic strokes are just the top of an iceberg. Namely, silent brain infarcts and white matter changes called as leukoaraiosis are common findings among stroke patients and patients without other findings in brain imaging. Recently, these neuroimaging findings have been observed in younger stroke patients, as well. (4) In this MD-thesis project, current literature regarding leukoaraiosis and silent brain infarcts are reviewed and features of these changes in young patients with first-ever ischemic stroke are elucidated.
2 Literature review

2.1 Silent brain infarcts (SBI)

Silent or subclinical strokes differ from symptomatic brain infarcts in lack of stroke-like symptoms. Thus patients with subclinical stroke do not notice any symptoms that relate to stroke. Prevalence and incidence of silent brain infarcts increase steeply with age and their frequency in older patient groups is approximately 20%. Silent brain infarcts are associated with an increased risk of stroke and the presence of silent brain infarcts increases the risk of a new silent infarct 3-fold. Silent infarcts have also value in predicting subsequent risk of vascular dementia. The prevalence of silent brain infarcts is five times greater than prevalence of the symptomatic strokes and underlying etiology is considered partly different. In young adults, the implications and prognostic value of silent brain infarcts and leukoaraiosis are, however, not yet clarified and may not be fully similar as in elderly populations.

Incidence of silent brain infarcts particularly in a population under fifty years old has not been studied earlier but it is estimated to be lower than in elder population. In previous community-based and population-based studies involving mostly elderly patients, the reported prevalence on silent brain infarcts on MRI have ranged between 8 to 28%, depending mainly on age. In South-Korean study the prevalence of SBIs in those aged 20 to 39 was 0% and 1.7% in those aged 40 to 49. In Framingham Offspring Study the prevalence of SBIs among those aged 30 to 49 was less than 8%. The prevalence of SBIs in older Japanese patients (mean age 69) with first-ever ischemic stroke was as high as 57%, which correlates well with the fact that the frequency of SBIs increases steeply along aging. However, small-vessel disease is very common in Japanese population and it is known to associate strongly with SBIs. In the Rotterdam Scan Study the researchers discovered that subclinical brain infarcts and white matter changes in brain are independent risk factors for symptomatic stroke in general adult population and the result can not be explained by the risk factors of symptomatic stroke.
Risk factors and etiology of silent brain infarcts is incompletely understood. The cardiovascular risk factors for silent brain infarcts such as high age, the presence of diabetes mellitus, increasing intima-media thickness and metabolic disorder are estimated to be the same as for symptomatic stroke. (11)

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>References of studies finding association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>10-17</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>10, 15</td>
</tr>
<tr>
<td>Family history of stroke</td>
<td>16</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>15, 17</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10, 14-16</td>
</tr>
<tr>
<td>Diabetes</td>
<td>14</td>
</tr>
<tr>
<td>Carotid stenosis</td>
<td>15</td>
</tr>
<tr>
<td>Intima-media thickness</td>
<td>11</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>17</td>
</tr>
<tr>
<td>Smoking</td>
<td>16</td>
</tr>
<tr>
<td>Alcohol</td>
<td>18</td>
</tr>
<tr>
<td>Hyperhomocysteinaemia</td>
<td>14, 19</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>20</td>
</tr>
<tr>
<td>Creatinine</td>
<td>15, 17, 21</td>
</tr>
<tr>
<td>Cystatin C</td>
<td>21</td>
</tr>
<tr>
<td>Migraine</td>
<td>13</td>
</tr>
<tr>
<td>Retinal microvascular abnormalities</td>
<td>22</td>
</tr>
<tr>
<td>Prevalent silent brain infarct</td>
<td>11</td>
</tr>
<tr>
<td>Severe white-matter lesions</td>
<td>14, 17</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>23</td>
</tr>
</tbody>
</table>

*Table 1. Risk factors for MRI-defined silent brain infarcts; adapted from Vermeer et al. (7) This table takes into account only studies that find a clear association.*

Silent cerebral infarctions differ from symptomatic strokes also in size and location. Subclinical infarcts are usually small, deep and often situated in the basal ganglia. In the
Rotterdam Scan Study researchers detected silent lacunar infarcts in the basal ganglia in 80% of the patients with silent infarcts. Furthermore, 33% of symptomatic strokes were situated cortically, whereas only 5% of the patients with silent infarcts had them situated in the cortex. (10) The location of silent cerebral infarctions was also noticed to be considerably different than that for the symptomatic infarction in the TOAST study. (24) They found out that there was more asymptomatic infarcts situated in the occipital lobe and basal ganglia and less clinically silent lesions in frontal, temporal and parietal lobes, internal capsule and corona radiata. (24)

Silent infarcts are also frequently smaller than symptomatic strokes in all studies. In the Rotterdam Scan Study, over 94% of the silent infarcts were lacunar. Furthermore, symptomatic lacunar infarcts were larger than the asymptomatic ones. (25)

Figure 1. T1-weighted MRI showing silent cortical infarct in the left temporo–occipital lobe (A), and a silent lacunar infarct in the right thalamus (B). (7)

The term “lacunar infarct” refers to a radiological definition and does not necessarily correlate with underlying stroke etiology. (26,27) Lacunar infarcts are small deep infarcts with a diameter of 2-20mm. A quarter of all ischemic strokes are lacunar type. This leads us back to the pathogenesis of silent brain infarcts because lacunar infarcts
are caused mainly by small-vessel disease occluding a small perforating artery supplying the subcortical areas of the brain. A Japanese study discovered that silent subcortical infarcts are frequently lacunar and based on that they hypothesized that the pathogenesis of silent subcortical ischemic brain lesions is common to that of lacunar infarction meaning small-vessel vasculopathy. (9)

Autopsy studies have revealed two types of underlying small-vessel pathologies. Microatheromatosis is associated with single or a few larger lacunar infarcts without leukoaraiosis and it is situated usually at the origins or proximal portions of the larger (200-800 µm in diameter) perforating arteries. Lipohyalinosis, which appears as an eosinophilic deposit in the connective tissue of the vessel wall, presents as a diffuse arteriopathy of the smaller perforating arteries and is mainly associated with small, multiple and asymptomatic brain infarcts. It is also closely associated with endothelial dysfunction thus these lesions are postulated to occur secondary to damaged cerebrovascular autoregulation. Furthermore, periventricular leukoaraiosis is caused by lipohyalinosis of white matter perforating small arteries. Hypertension, age, diabetes and smoking are the main risk factors for lipohyalinosis, where as age, diabetes, hypercholesterolemia, smoking and myocardial infarction correlate better with cerebral large vessel disease (LVD). (25, 28) Diabetes mellitus is characterized by both microvascular and macrovascular pathology so it is obvious that it is associated with both large- as well as small vessel disease.

In contrast to lacunar ischemic stroke, which is due to an intrinsic cerebral small arteriolar abnormality, cortical ischemic stroke is commonly due to embolism from the heart or large arteries. Nevertheless intracranial large artery atheromatous stenoses and other common causes of large artery infarction such as emboli appear to cause more than 10-15% of lacunar strokes. (29) The etiology behind lacunar strokes and large cortical stroke seems to be different. After lacunar ischemic stroke, a recurrence is more likely to be lacunar then cortical stroke. As mentioned above, silent lacunar infarcts increase the risk of stroke but at same time they increase the risk of new silent infarct by three fold. Furthermore, white matter lesions, that are also called leukoaraiosis, appear to be more closely associated with lacunar ischemic stroke than with cortical stroke.
2.2 Leukoaraiosis (LA)

Cerebral white matter (WM) surrounds the subcortical gray matter (GM). It consists of axons and their myelin sheaths. White matter contains less water and more lipid than the GM. Cerebral blood in the white matter is only 25% (20ml/100g/min) from the blood flow per minute in the gray matter (80ml/100g/min). (30) The major function of the white matter is to provide neurons with structural support, maintain local conditions for neuronal function and to interconnect various regions of brain and transmit signals in-between them. White matter of the brain is developed from the external marginal zone of neural tube and it forms approximately half of the brain weight and volume. (31)

Cerebral white matter changes (WMC) are a common feature in the brain caused by aging but they are also found in a number of diseases of adulthood. Pathological white matter changes can be found in debated Binswanger’s disease, multiple sclerosis, acute demyelinating encephalomyelitis, posterior reversible leukoencephalopathy syndrome, cerebral anoxia, leukodystrophies, and mitochondrial encephalopathies, among others. Leukoaraiosis is also widely found in dementing illnesses, such as Alzheimer’s disease, vascular dementia, and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy such as cerebral autosomal dominant arteriopathy (CADASIL). (32)

White matter changes, i.e. leukoaraiosis, refers usually to nonspecific white matter changes. They can be detected primarily in the elderly and the lesions can not be attributed to a specific disease. Leukoaraiosis comes from Greek words “leuko” meaning white and “araios” signifying rarefied or rarefaction. (33) These white matter changes in brain appear hypointense on CT (computer tomography) scans because of reduced X-ray attenuation and hyperintense on T2-weighted MRI (magnetic resonance imaging). (34) Size, shape and location varies. Leukoaraiosis can be focal, patchy or diffuse area in the white matter and it is situated periventricularly or deeper in the white matter. Mild degree of leukoaraiosis is considered to be a normal finding in the brain of elderly people. However, evidence has also accumulated showing that moderate-to-severe white matter changes are correlated with motor and gait disturbances, depressive
symptoms, urinary disturbances and cognitive deficits. (35-37) Nevertheless, cognitive deficits are likely to be associated with lesions such as lacunar infarcts and coexisting degenerative diseases. (38) It is worth noticing that some individuals, regardless of the severity of leukoaraiosis, remain neurologically and neuropsychologically asymptomatic for prolonged periods while others develop major symptoms mentioned above.

Leukoaraiosis increases mortality and risk of dementia. (39-42) The presence of leukoaraiosis increases the risk of small-vessel strokes, vascular mortality, intracerebral bleeding in patients on anticoagulation, bleeding in patients undergoing carotid artery surgery, predicts poorer clinical outcome in patients with infratentorial stroke, increases risk of dementia and transition to disability. (35) Leukoaraiosis also predicts infarct size growth in acute ischemic stroke. (43) Because of reasons mentioned above, leukoaraiosis is considered as a marker of poor prognosis.

Autopsy studies of the brain with leukoaraiosis have revealed that the lesions are strongly associated with arteriolar tortuosity, lacunar infarcts and incomplete infarctions as well as periventricular venous collagenosis, perivascular degeneration with widening of extracellular and perivascular spaces. Leukoaraiosis is also characterized with endothelial dysfunction, prothrombic changes like increased platelet activation and hypercoagulability and decline in cerebral perfusion. (44) Thus, it is thought to be a marker of compromised tissue perfusion because it is associated with a number of structural and functional vascular changes such as arteriosclerotic narrowing, elongation, tortuosity and impaired autoregulation. Resting cerebral blood flow is reduced up to 30% in brains with extensive leukoaraiosis. (43) Chronic ischemia and the increase in water content of the affected brain cause axonal loss and thus leads to inflammatory reaction, changes in myelin and compromised axonal transport. The structure of the white matter thins out in areas with leukoaraiosis because of apoptosis and gliosis. This leads to proliferation of glial cells and therefore gradual expansion of the lesions. (7)
Thus, leukoaraiosis is associated with factors that modulate tissue perfusion as well as tissue capacity for handling of ischemia. Leukoaraiosis is a composite product of multiple factors which themselves seem to play a role in determining the tissue outcome after ischemia. (43) The heritability of leukoaraiosis volume is detected to be 55% in general population and higher among women (78%) than among men (52%). (45) Thus, genetic variation is thought to play a major role in interindividual variation in leukoaraiosis volume.

Leukoaraiotic lesion also appear to progress over time as well as the number of silent lacunar infarcts. Factors that seem to induce progression of leukoaraiosis are history of diabetes, high blood glucose and history of stroke. Progression is usually evidently situated in the subcortical white matter where white matter changes are also most common at baseline. The volume of leukoaraiosis at baseline and an increase of existing white matter changes correlate most significantly to the progression of leukoaraiosis. (46)

Leukoaraiosis is a radiological finding and its pathogenesis or clinical significance is not well acknowledged. T2-weighted imaging is sensitive to liquid, gliosis and the effects of demyelination. FLAIR images are heavily T2-weighted with cerebrospinal fluid suppression. This makes it possible to detect also leukoaraiotic lesions situated close to the cerebrospinal fluid and to differentiate Virchow-Robin spaces from leukoaraiosis. The decline in cerebral blood flow in areas with leukoaraiosis can be detected with imaging techniques such as average apparent diffusion coefficient (ADCAv) where tissues with faster diffusion appear bright and tissues with slower diffusion dark. Normally axons produce significant hindrance to water diffusion but leukoaraiosis causes axonal loss and furthermore leads to an increase in water content of the tissue which can be detected with these imaging techniques. DWI (diffusion-weighted MRI) makes it possible to differentiate acute and chronic ischemic stroke lesions from leukoaraiosis. In DW images, tissues with faster diffusion appear dark and tissues with slower diffusion bright. (47)
To date, almost all stroke patients undergo brain imaging at least with computed tomography (CT) as they arrive at the hospital. In recent years an increasing amount of patients and especially young patients are being imaged also by MRI (magnetic resonance imaging), which makes the leukoaraiosis research easier because MRI is much more sensitive to leukoaraiotic changes than CT. Frequency of leukoaraiosis in older patient groups has ranged between 21% and 100% and in healthy subjects, it is found in 1-27% depending on the imaging method used and on the study population. Various rating scales also exist between studies. Some make a distinction between different regions, whereas others use an overall estimate of leukoaraiosis.
3 Patients and methods

This study was approved by the relevant authorities and performed at the Department of Neurology, Helsinki University Central Hospital. We included patients involved in the Helsinki Young Stroke Registry, (4) from 1994 to 2007, who had undergone an initial brain MR scan at 1.0 or 1.5 teslas. The patients were originally found by computer search of the hospital’s electronic database according to the following criteria: discharge diagnosis of an ischemic stroke, age 15–49 years at stroke onset, and patient living in the catchment area of the hospital. Only patients with first-ever ischemic stroke were included in the registry. In addition to those with false primary diagnosis, we excluded patients with transient ischemic attack (TIA), cerebral venous thrombosis, stroke due to direct head trauma or strangulation, ischemic lesion due to immediate complications originating from subarachnoidal hemorrhage, and any iatrogenic stroke as a consequence of angiographic imaging or major surgery. Of the 1,194 consecutive patients found by the computer search, 1,008 were included in the registry, and of these, 671 patients were initially scanned with MRI. Of the MR-scanned patients, 669 had complete imaging data, being eligible for the present study. They represented well the entire cohort of 1,008 patients.

We obtained demographic and risk factor data from the medical records. The definitions of risk factors were based on information available before the onset of the stroke, and on all poststroke diagnostic testing related to the current stroke. All patients underwent routinely a range of laboratory testing, which are described in detail elsewhere. (4) Family history of any stroke was defined as history of ischemic or hemorrhagic stroke, or TIA, in a first-degree relative. Dyslipidemia was defined as treated with lipid-lowering medication or total cholesterol level $\geq 5.0$ mmol/L (193 mg/dL), low-density lipoprotein level $\geq 3.0$mmol/L (116 mg/dL), or high-density lipoprotein level <1.0mmol/L (39 mg/dL). Hypertension was defined as treated with antihypertensives, or a history or present diagnosis of hypertension according to the 2003 World Health Organization criteria as systolic blood pressure $\geq 140$ mm Hg and/or diastolic blood pressure $\geq 90$ mmHg. A patient was considered as current smoker if smoking regularly $\geq 1$ cigarettes per day within the year before stroke. We defined obesity as body mass...
index (BMI) ≥30 kg/m² or patient clearly stated as heavily obese if BMI data were not available. Cardiovascular disease was defined as any of coronary heart disease, heart failure, myocardial infarction, or peripheral arterial disease. Diabetes mellitus type 1 and 2 were separately registered and defined as treated or presently diagnosed according to the 1999 World Health Organization criteria as fasting plasma glucose ≥7.0 mmol/L (126 mg/dL). In Finland, children and young adults with newly diagnosed type 1 diabetes are almost invariably diagnosed and treated in hospital, and the diagnosis is based on clinical characteristics, C-peptide measurements, and where necessary, glutamate decarboxylase antibody measurements. The type of diabetes is thus reliably distinguished based on information obtained from the medical records. Other registered risk factors were chronic or paroxysmal atrial fibrillation, and migraine, the latter defined according to the International Headache Society criteria. (48)

We classified stroke subtypes according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria. (49) A pair of investigators assigned the stroke subtype to each patient, and in case of discrepancy, the patient records were reviewed by a senior investigator and the final categorization was based on a consensus agreement of all three.

All brain imaging studies were originally interpreted by neuroradiologists. Analysis and rating of SBIs and leukoaraiosis were performed by study stroke neurologists and senior neuroradiologist (O.S.) blinded to clinical data. We defined SBI as focal hyperintensity on T2-weighted images, 3 mm in size or larger, and without a history of corresponding neurologic symptoms or signs. To distinguish infarcts from leukoaraiosis, infarcts had to have corresponding hypointensity on T1-weighted images. We measured the diameter of each SBI in millimeters using axial images and registered brain side, as well as calculated the number of SBIs for each patient. Localization of each SBI was classified as follows: cortical, cerebellum, brainstem (including pons), thalamus, lacune subcortical, and lacune basal ganglia. Leukoaraiosis was defined as hyperintense lesions in periventricular or subcortical regions, or in pons, on fluid-attenuated inversion recovery MRI sequences, and, in two patients, on T2-weighted sequences. We evaluated leukoaraiosis according to a previously validated visual rating scale developed in our
hospital. (50) The reliability of rating have been tested and found to be good (intraobserver agreement, weighted $\kappa=0.90–0.95$; interobserver agreement, weighted $\kappa=0.72–0.84$). (50) Periventricular hyperintensities (PVHs) around frontal and occipital horns, along the bodies of lateral ventricles, and in regions other than periventricular white matter were classified and scored based on shape and size of the lesions (table 1). Presence of pontine leukoaraiosis was additionally scored. Scores of these four components were added up for each patient, and the sum score was categorized into mild (1–4), moderate (5–8), or severe (9–12). Presence of leukoaraiosis was thus defined as any score greater than zero.

Chi-square and Fisher exact tests allowed comparisons of categorical variables between the groups. The Student $t$ test was used for comparisons of means, and the Mann–Whitney $U$ test was used for ordinal variables. Historic risk factor information based on self-reporting (migraine, smoking, and family history of stroke) that was not mentioned in the medical records was considered as being not present. Otherwise, there were no missing values in risk factor variables. All statistical analyses used SPSS 15.0 for Microsoft Windows (SPSS Inc., Chicago, IL). Two-sided values of $p<0.05$ were considered significant.
**From the left:** a. Small caps around the frontal horns of lateral ventricles. b. Large caps. c Extending caps.

d. Thin lining along the bodies of the lateral ventricles. e. Smooth halo. f. Irregular halo

g. Multiple small focal lesions h. Multiple large focal lesions i. Multiple focal confluent lesions

j. Diffusely confluent lesions irregular in shape k,l. Extensive WM changes

**Figure 2.** Periventricular white matter changes (a-f) and white matter changes in regions other than the periventricular area (g-l) (FLAIR images) (31)
### Table 1. Characteristics of Patients with MRI-Defined Leukoaraiosis, Leukoaraiosis Score, and Features of Silent Infarcts in These Patients (N=50).

| Characteristics                                                                 | Absent (0) | Small cap (1) | Large cap (2) | Extending cap (3) | Absent (0) | Thin lining (1) | Smooth halo (2) | Irregular halo (3) | Absent (0) | Small focal lesions (1) | Large focal lesions (2) | Focal confluent lesions (3) | Diffusely confluent lesions (4) | Extensive white matter change (5) | Absent (0) | Present (1) | Mean (±SD) | Median | Range | Males, median score | Females, median score | Mild to moderate (1-6) | Severe (7-12) | Present | Average size, mm | Cortical | Cerebellar | Brainstem | Thalamus | Lacune subcortical | Lacune basal ganglia |
|----------------------------------------------------------------------------------|------------|---------------|---------------|------------------|------------|-----------------|-----------------|-------------------|------------|------------------------|--------------------------|--------------------------|----------------------------|------------------|-------------|-------------|-------------|------------|-------------|---------------------|
| Periventricular hyperintensities (PVH) around frontal and occipital horns (score)|            | 24 (48)       | 17 (34)       | 8 (16)           | 1 (2)      | 38 (76)         | 7 (14)          | 4 (8)             |            | 9 (18)                 | 13 (26)                  | 9 (18)                  | 10 (20)                      | 8 (16)           | 1 (2)       | 43 (86)     | 7 (14)      |            |             |         |
| PVH along the bodies of lateral ventricles (score)                                |            |               |               |                  | 1 (2)      |                 |                 |                   |            |                        |                          |                          |                             |                 | 43 (86)     | 7 (14)      |             |            |             |         |
| Hyperintensities in the regions other than periventricular white matter (score)  |            |               |               |                  | 9 (18)     | 13 (26)         | 9 (18)          |                   |            | 9 (18)                 | 13 (26)                  | 9 (18)                  | 10 (20)                      | 8 (16)           | 1 (2)       |            |             |            |             |         |
| Pontine leukoaraiosis (score)                                                    |            | 43 (86)       | 7 (14)        |                  |            |                 |                 |                   |            |                        |                          |                          |                             |                 |            |             |             |            |             |         |
| Leukoaraiosis score (0-12)                                                       |            | 5.0 (±2.1)    |               |                  |            |                 |                 |                   |            | 5.0 (±2.1)             | 5 (±2.1)                 | 5 (±2.1)                 | 4 (±2.1)                      | 4 (±2.1)         | 36 (72)    | 14 (28)    | 17 (34)    | 10 (±7)   |             |         |
| Silent brain infarcts                                                            |            | 17 (34)       |               |                  |            |                 |                 |                   |            |                        |                          |                          |                             |                 |            |             |             |            |             |         |
| Silent brain infarct location                                                     |            |               |               |                  |            |                 |                 |                   |            |                        |                          |                          |                             |                 |            |             |             |            |             |         |

Data are expressed as n (%) or mean (±SD).
4 Results

Of the 669 patients included, 86 (13%) had one or more SBIs and 50 (7%) had leukoaraiosis. Among these, 17 (3%) had both findings. In total, 550 (82%) patients were free of SBIs and leukoaraiosis, serving as a control group. In the study population, SBIs began to appear at age 26 years and leukoaraiosis began to appear at age 35 years, whereas the proportion of patients free of SBIs and leukoaraiosis strikingly decreased with aging (figure 3).

![Figure 3. Proportions of Patients with MRI-defined Silent Brain Infarcts (SBI) or Leukoaraiosis as a Function of Age in the Patient Cohort (N=669).](image-url)
We identified a total of 276 SBIs in our patients. The majority (n = 46, 54%) had only a single lesion, 17 (20%) had two lesions, and 23 (27%) patients had three or more lesions. SBIs were located mostly in basal ganglia and subcortical regions, but silent lesions in cerebellum were rather frequent as well (figure 4).

**Figure 4.** Locations of MRI-Defined Silent Brain Infarcts and Average Size of Lesions in Each Location.

The majority of patients had right-sided SBIs (n = 37, 43%), whereas 22 patients (26%) had left-sided lesions, and 27 patients (31%) had bilateral SBIs. The average SBI diameter was 9 mm, ranging from 3 to 83 mm, the latter in a 46-year-old man with an SBI in the right frontotemporal cortex. Most patients with leukoaraiosis had mild to moderate changes. Males had a slightly higher leukoaraiosis score (mean score 5.4 ± 2.0 vs 4.7 ± 2.2, p = 0.217). SBIs were located mainly in basal ganglia in those 17 with concurrent leukoaraiosis and SBIs. PVHs around frontal and occipital horns most often appeared in the forms of a small or large cap. PVHs along the bodies of lateral ventricles were mostly characterized by thin lining. Hyperintensities in regions other than periventricular white matter varied the most from small focal lesions to extensive
white matter change, the latter in a patient with a long history of untreated grave hypertension and acute presentation of hypertensive encephalopathy and ischemic stroke (Table 1). Stroke risk factors and etiology of the first-ever overt stroke in the study population are shown in Table 2.

Table 2. Demographic Data, Risk Factors, and Subtypes of Clinically Overt Brain Infarcts in the Study Population and Patients with MRI-Defined Silent Brain Infarcts (SBI), and Leukoaraiosis Compared with Controls Free of These Findings.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Overall (N=669)</th>
<th>Controls (n=550)</th>
<th>SBI Present (n=86)</th>
<th>LA Present (n=50)</th>
<th>SBIs and Leukoaraiosis (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>39.9 (±8.0)</td>
<td>39.1 (±8.3)</td>
<td>43.1 (±6.0)**</td>
<td>45.4 (±4.0)**</td>
<td>46.4 (±3.4)**</td>
</tr>
<tr>
<td>Males</td>
<td>389 (58)</td>
<td>317 (58)</td>
<td>56 (65)</td>
<td>25 (50)</td>
<td>9 (53)</td>
</tr>
<tr>
<td>Family history of any stroke</td>
<td>88 (13)</td>
<td>72 (13)</td>
<td>10 (12)</td>
<td>9 (18)</td>
<td>3 (18)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>372 (56)</td>
<td>293 (53)</td>
<td>57 (66)*</td>
<td>30 (60)</td>
<td>8 (47)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>247 (37)</td>
<td>181 (33)</td>
<td>47 (55)**</td>
<td>33 (66)**</td>
<td>14 (82)**</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>266 (40)</td>
<td>210 (38)</td>
<td>43 (50)*</td>
<td>23 (46)</td>
<td>10 (59)</td>
</tr>
<tr>
<td>Obesity</td>
<td>62 (9)</td>
<td>40 (7)</td>
<td>14 (16)*</td>
<td>10 (20)*</td>
<td>2 (12)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>46 (7)</td>
<td>31 (6)</td>
<td>12 (14)*</td>
<td>7 (14)*</td>
<td>4 (24)*</td>
</tr>
<tr>
<td>Diabetes mellitus, type 1</td>
<td>29 (4)</td>
<td>13 (2)</td>
<td>10 (12)**</td>
<td>10 (20)**</td>
<td>4 (24)*</td>
</tr>
<tr>
<td>Diabetes mellitus, type 2</td>
<td>37 (6)</td>
<td>25 (5)</td>
<td>9 (11)*</td>
<td>3 (6)</td>
<td>0</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>19 (3)</td>
<td>16 (3)</td>
<td>2 (2)</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Carotid stenosis &gt;25%</td>
<td>37 (6)</td>
<td>24 (4)</td>
<td>8 (9)</td>
<td>9 (18)*</td>
<td>4 (24)*</td>
</tr>
<tr>
<td>History of migraine</td>
<td>138 (21)</td>
<td>122 (22)</td>
<td>13 (15)</td>
<td>4 (8)*</td>
<td>1 (6)</td>
</tr>
</tbody>
</table>

Etiology of the first-ever overt ischemic stroke (TOAST classification)

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Overall (N=669)</th>
<th>Controls (n=550)</th>
<th>SBI Present (n=86)</th>
<th>LA Present (n=50)</th>
<th>SBIs and Leukoaraiosis (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large-artery atherosclerosis</td>
<td>37 (6)</td>
<td>22 (4)</td>
<td>10 (12)*</td>
<td>8 (16)*</td>
<td>3 (18)*</td>
</tr>
<tr>
<td>Cardioembolism</td>
<td>118 (18)</td>
<td>98 (18)</td>
<td>16 (19)</td>
<td>6 (12)</td>
<td>2 (12)</td>
</tr>
<tr>
<td>Small-vessel disease</td>
<td>91 (14)</td>
<td>51 (9)</td>
<td>27 (31)**</td>
<td>22 (44)**</td>
<td>9 (53)**</td>
</tr>
<tr>
<td>Other determined etiology</td>
<td>193 (29)</td>
<td>173 (32)</td>
<td>16 (19)*</td>
<td>7 (14)*</td>
<td>3 (18)</td>
</tr>
<tr>
<td>Undetermined etiology</td>
<td>230 (34)</td>
<td>206 (38)</td>
<td>17 (20)*</td>
<td>7 (14)*</td>
<td>0</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD or n (%).
* P<0.005; **P<0.001

TOAST, Trial of Org 10172 in Acute Stroke Treatment.

As expected, patients with SBI, leukoaraiosis, or both were older compared with controls free of these findings. Hypertension, both types of diabetes, cardiovascular disease, obesity, smoking, and dyslipidemia were more frequent in patients with SBIs.
compared with controls. In patients with leukoaraiosis, hypertension, obesity, type 1 diabetes mellitus, and cardiovascular disease were more common. SBIs and leukoaraiosis clearly were more often present in patients with first-ever overt infarct associated with small-vessel disease or large-artery atherosclerosis, and less common in those with other determined or undetermined etiology. In patients with SBIs, the specific causes of stroke in the other determined category (TOAST 4) were as follows: primary angiitis of the central nervous system (PACNS) (n = 5), cervical artery dissection (4), hypertensive encephalopathy (2), factor V Leiden mutation (2), (CADASIL) (1), systemic lupus erythematosus (SLE) (1), and radiation vasculopathy (1). Accordingly, leukoaraiosis was found in those with PACNS (n =2), CADASIL (2), hypertensive encephalopathy (1), SLE (1), and radiation vasculopathy (1). (Females tended to have an increased risk for leukoaraiosis; otherwise, we observed no clear sex preference. Hypertension had only a trend-like association with both SBIs and leukoaraiosis alone. In addition to increasing age, smoking, hypertension, and in particular type 1 diabetes were independent predisposing factors in those with concurrent SBIs and leukoaraiosis.)
5 Discussion

SBIs and leukoaraiosis were common findings among our young stroke patients. SBIs were seen already in early adulthood, whereas leukoaraiosis began to appear at early midlife. Apart from increasing age, juvenile-onset diabetes mellitus was the strongest risk factor for both SBIs and leukoaraiosis in this young patient population.

In our young patients, the prevalence of SBIs and leukoaraiosis increased with aging and occurred in parallel with the exponentially increasing occurrence rate of first-ever overt ischemic stroke. (4) More than one-fourth among patients aged 45–49 years and nearly one-fifth among patients aged 40–44 years had SBIs, leukoaraiosis, or both (figure 1). In previous community-based and population-based studies involving mostly elderly persons, the reported prevalences of SBIs on MRI have ranged from 8% to 28% and have depended mainly on age. (7) Two studies have documented the prevalence of SBIs in detail in healthy middle-aged subjects: the prevalence among younger participants was 0% in those aged 20–39 years and 1.7% in those aged 40–49 years in a South Korean study, (8) and <8% among those aged 30–49 years in the Framingham Offspring Study. (51) The prevalence of MR-defined SBIs in older Japanese patients (mean age 69 years) with first-ever ischemic stroke was 57%. (9) This high percentage may well correlate with our observations of the steeply increasing frequency of SBIs with aging. However, Japanese are known to have a high frequency of small-vessel disease, which associates strongly with SBIs.

Akin to previous studies, which have enrolled mostly elderly persons, (8, 10,13,15, 51-53) most SBIs in our patients were located in subcortical deep white matter and basal ganglia, which thus reflect the probable underlying small-vessel pathology. However, we observed a considerably higher proportion of silent cerebellar infarcts (15%) in our young patients compared with that registered in the healthy elderly (1%–8%) (8, 10, 15, 51, 52) or in patients with acute ischemic stroke scanned with CT (7%). (24) Migraine was suggested as an independent risk factor particularly for cerebellar silent ischemic lesions in the general population. (54) In contrast, we did not find such association in our young stroke patients. Thus we find it possible that the association between
migraine and young patients with SBIs in studies is due to the fact that migraine appears more often in young. Compared with our series, participants in that study (54) were older, and only four were younger than 50 years, which probably reflects that increasing age is the major predisposing factor for SBIs in migraineurs as well. Silent cardioembolism may in part explain the frequency of cerebellar SBIs in our patients, because those with identified cardioembolic source underlying the overt stroke were rather numerous. As observed, younger stroke patients tend to have more frequently overt posterior territory ischemia and cerebellar infarcts. (4) This observation, jointly with the frequency of cerebellar SBIs, might reflect the same—yet unclear—pathophysiologic mechanisms. The observed side preference of SBIs likely reflects the fact that symptoms arising from lesions in the nondominant hemisphere are not well recognized even in the young. (4)

Leukoaraiosis is increasingly apparent after age 50 years, and the prevalence is very high in elderly populations. (12, 14, 55, 56) In mostly older patients with TIA or stroke, leukoaraiosis was present in 44%. (57) A community-based Japanese study revealed a prevalence of a few percent in participants in their 40s. (14) In our study, the prevalence was 6% both in patients aged 35–39 years and in those aged 40–44 years but doubled in the age group of 45–49 years, which reflects that age is also the major determinant for leukoaraiosis. (58) We used a leukoaraiosis rating scale that takes into account the number, size, and shape of leukoaraiotic lesions. (31) According to our simple scoring system—considering all white matter areas and brainstem—our young patients had mostly mild to moderate leukoaraiotic changes, whereas males had slightly more severe lesions. The latter is opposite to the trend observed in the general population. (55) However, our relatively small number of patients with leukoaraiosis may not allow firm conclusions on this issue.

Silent myocardial infarctions are frequently seen among patients with type 1 diabetes, (59) but to our knowledge, the strong associations between type 1 diabetes and early-onset SBIs or leukoaraiosis have not been previously observed. Results on the association of type 2 diabetes with both SBIs and leukoaraiosis in elderly populations have been conflicting. (7, 14, 51, 52, 58, 60) This may be due to weak associations,
small sample sizes, or a combination of both. Interestingly, the well-established associations between hypertension and SBIs (7) and leukoaraiosis (60) were not that clear in our series, and were only seen in those with coexistent SBIs and leukoaraiosis, who also were older. Likely explanations for these observations are that in younger patients, hypertension may not have had enough time to cause advanced vessel pathology, whereas juvenile-onset diabetes and chronic hyperglycemia may have altered the endothelial function, leading to early atherosclerosis, possibly for years or decades before stroke. (61)

Recently, there has been a growing attention on the association between metabolic syndrome, its components, and SBIs (23) as well as leukoaraiosis. (62) This association is also obvious in our series, because obesity was related with the presence of both SBIs and leukoaraiosis. Smoking was associated with SBIs only in two prior studies, (7) but its relation to pathogenesis of leukoaraiosis or small-vessel disease is even more controversial. (28, 58) Accordingly, in our young patients, smoking was associated with SBIs but not with leukoaraiosis. However, as with hypertension, smoking was clearly associated with coexistent SBIs and leukoaraiosis.

Small-vessel disease is the most likely stroke subtype associated with the presence of both SBIs (7) and leukoaraiosis. (57) Given the overall high frequency of vascular risk factors in our patients, (4) those with non-small-vessel disease related stroke also may harbor risk factors predisposing to small-vessel pathology. This is obvious particularly in those with large-artery atherosclerosis. In addition, SBIs may well be related to conditions such as cervical artery dissection or PACNS per se, considering their pathophysiologic mechanisms and often slowly or gradually evolving pathogenesis. (63, 64) Both SBIs and leukoaraiosis are characteristic even in younger patients with CADASIL. (65)

Our study has several limitations. It covers a long time period and is subject to variability in MR technology. We may have misclassified a few SBIs because of incomplete patient history information or because some patients may not recall their stroke symptoms or correctly interpret all their previous symptoms. The Helsinki Young
Stroke Registry includes only patients younger than 50 years and with first-ever ischemic stroke, reducing this possibility. Approximately one-third of our patients in the registry were scanned only with CT and were excluded from the present study, which may have led to slight underestimation of small SBIs in the entire cohort of 1,008 consecutive patients. However, including only MR-scanned patients was reasonable because sensitivity to detect and classify infarcts on MRI is clearly better than on CT. (7) Because of the study design, we may have underestimated the prevalence of some historic risk factors, such as smoking or family history of stroke. Numbers of patients particularly in the leukoaraiosis and combined SBI and leukoaraiosis groups were relatively small, (which should be taken into account when interpreting the results of the multivariate analyses.) Finally, because we included only stroke patients, the issue of whether the observed risk factor associations also are present in young people without any history of an overt stroke should be tested in large-scale studies.
6 Conclusions

Based on previous community-based and population-based studies involving mostly elderly patients silent brain infarcts and white matter changes called as leukoaraiosis are common findings among stroke patients and patients without other findings in brain imaging. However they do not appear to be very uncommon findings among young adults either. Silent brain infarcts appear as focal hyperintensity in brain on T2-weighted images without a history of corresponding neurologic symptoms or signs. To distinguish infarcts from leukoaraiosis, infarcts have corresponding hypointensity on T1-weighted images. Leukoaraiosis can be detected as hyperintense lesions in periventricular or subcortical regions, or in pons, on fluid-attenuated inversion recovery MRI sequences or respectively on T2-weighted sequences.

The most widely accepted risk factors for silent brain infarcts are cardiovascular risk factors such as high age, the presence of diabetes mellitus, obesity and smoking. Furthermore, the most essential risk factors for leukoaraiosis are type 1 diabetes, obesity, female sex, and increasing age. Not to mention that small-vessel disease is the predominant cause of stroke in both groups. Silent brain infarcts are associated with an increased risk of stroke, a new silent brain infarct and vascular dementia. Furthermore, leukoaraiosis appear to be more closely associated with lacunar ischemic stroke than with cortical stroke. Leukoaraiosis alone is correlated with motor and gait disturbances, depressive symptoms, urinary disturbances, cognitive defects, increased mortality, poorer clinical outcome of stroke, transition to disability and overall poor prognosis. Thus it is very important to find patients with silent brain infarcts and/or leukoaraiosis. This group of people, particularly young adults, would benefit from more frequent medical monitoring and aggressive prevention of stroke and dementia. Furthermore this kind of prevention therapy requires prolonged monitoring which would benefit from persistent relationship between patient and nursing staff.
6 References


