COMMENTARY

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Silent Brain Infarction — Time for Changing the Paradigm?

Silent brain infarctions have received a lot of attention in recent years, and much data has been accumulating on its epidemiology and impact. Current guidelines do not support population screening, or indeed, any "pre-emptive strike" if covert infarcts are discovered.[1] Indeed, no randomized controlled trials have yet been concluded to validate the efficacy and advantage of such an approach. However, pending further evidence, I present my viewpoint on this cutting-edge topic. The evidence nearly complies with criteria for screening of selected elderly populations[2] and already strongly suggests that a more active policy is warranted.

DEFINITION AND DIAGNOSIS

Defined as asymptomatic brain infarction identified by neuroimaging (magnetic resonance imaging [MRI] is distinctly more sensitive and specific than computed tomography [CT]), silent infarctions are an important component of covert cerebral small-vessel disease that also includes white matter hyperintensities and microbleeds.[3] The substantial variability in previous reports has markedly improved following a recent international collaboration focusing on definitions and neuroimaging standards. Thus, most silent brain infarcts (>90% in population studies) are in the basal ganglia or subcortical in location; 3-15 mm in size; wedge-like, ovoid, or irregular in shape; and with T2 hyper/T1 hypointensity signal similar to cerebrospinal fluid, reflecting tissue destruction and cavitation.[1] So called lacunar infarcts (although not all small infarcts become cavities), they are likely due to an occlusion of a small perforating arteriole (diameter <200 μm). Cortical or larger subcortical infarcts (~10%) may be more often associated with cardiac thromboembolism or large vessel atheroembolism (carotid, aortic arch) and not small vessel disease.

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Requests for reprints should be addressed to Ami Schattner, MD. Professor of Medicine, Faculty of Medicine, Hebrew University and Hadassah, Jerusalem, Israel.

E-mail address: amischatt@gmail.com

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PREVALENCE AND INCIDENCE

Followed far behind by meningiomas and cerebral aneurysms (~2.5%), silent brain infarctions are by far the most common incidental finding on MRI in prospective, population-based studies of individuals without a known prior stroke. Prevalence varies greatly with age distribution and the population studied. However, a remarkably similar mean prevalence of 10.7%-12.6% was found in 2 large MRI-based longitudinal population studies of 3930 subjects in their early 60s (mean age 62 years) who often had hypertension (37%-48%) or diabetes (9%-14%) but were relatively healthy. Most had a single infarct, but a decade later, the prevalence more than doubled.[4] Thus, 60- to 65-year-old individuals seem good candidates for timely intervention. Among selected populations of similar age, such as patients with cardiovascular risk factors, the prevalence of silent infarctions was much higher, usually 38%-43%.[4] The presence of silent brain infarctions independently increased the risk of subsequent symptomatic stroke by 3- to 5-fold (much higher in high-risk populations) and also of recurrent stroke and stroke-related death.[5] The development of additional new silent infarctions however, is much more common than overt stroke.[6] It was estimated that in 1 year, 0.77 million persons had symptomatic stroke in the United States compared with 11 million silent infarctions, a so called "underappreciated epidemic."[4]

ASSOCIATED HARM

Several significant adverse health outcomes have been associated with the presence of silent brain infarctions, challenging the prevailing concept of "watchful waiting" alone. Because almost 60% of patients presenting with first-ever ischemic stroke already have silent brain infarctions, it can be considered a stroke-heralding marker.[4] In addition to the frequent appearance of new silent infarctions and symptomatic stroke,[5] consequences include well-documented cognitive decline as well as incident dementia (>doubled risk), subtle neurological abnormalities such as gait unsteadiness, associated depression (silent brain infarctions were detected in ~50% of elderly patients with major depression), and a significant excess mortality risk (>tripled).[5,7,8]

RISK FACTORS

Community-based studies using logistic regression afford well-founded understanding of the risk factors associated with silent brain infarctions. In addition to the profound influence of age,[6] myriad modifiable vascular risk factors have been identified as increasing the risk of silent brain infarctions. They include hypertension (strongest predictor; especially systolic blood pressure, blood pressure variability, nondipping), diabetes and metabolic syndrome, macrovascular disease (eg, coronary, carotid), chronic kidney disease, cardiac dysfunction—even subclinical (worse diastolic function was associated with silent brain infarctions, whereas systolic dysfunction was related only to clinical stroke), obstructive sleep apnea, and smoking. Atrial fibrillation, associated with cardioembolic stroke, was not associated with silent brain infarctions. In addition, several biochemical risk markers have been implicated (eg, homocysteinemia, elevated C-reactive protein, NT-proB-type natriuretic peptide, and gamma-glutamyl transferase). The greater the number and severity of risk factors is, the greater the burden of silent brain infarctions.

PATHOGENESIS

As can be swiftly inferred from their anatomical locations, pathological research, associated risk factors, and MRI signal characteristics (usually, small cavitation, often with a hyperintense rim of gliosis), silent brain infarctions are mostly due to an in situ occlusion of small perforating arteries. Although not all silent brain infarctions are necessarily homogeneous in evolution, most are believed to share pathogenesis with atherosclerosis-mediated (symptomatic) ischemic strokes.[1,3]

IMPLICATIONS FOR TREATMENT

The finding of silent brain infarction would assume special importance if it could lead to effective interventions improving associated adverse health outcomes. Once identified, it can arguably be regarded as a covert but "bona fide" vascular event similar in impact to symptomatic cerebral events with whom it shares pathogenesis, therefore warranting full secondary prevention measures until proven otherwise. This particularly applies to de novo patients, who have neither symptomatic large artery disease nor atrial fibrillation and are thus devoid of treatment modalities proven to prevent future major adverse cardiovascular events (MACE). Although as yet we have no solid proof of efficacy, a whole gamut of safe and simple interventions with proven efficacy in secondary prevention suggests itself. They are likely to be beneficial, looking at the well-documented risk factors identified and the relatively safe, sensible interventions. Optimal lifestyle changes, high-intensity statins, adding aspirin and possibly low-dose colchicine, more aggressive control of hypertension (in particular) and diabetes will now be indicated. Initial results suggest beneficial effects of adding low-dose aspirin or statin treatment on the accrual of new silent brain infarctions, but large clinical trials are awaited.[3]

In conclusion, vast evidence has accumulated proving that silent brain infarctions are highly prevalent in the elderly, especially those with multiple cardiovascular risk factors, and are associated with serious focal (stroke) and diffuse (cognitive decline) central nervous system morbidity and with increased mortality.

Looking at this evidence, and acknowledging the current absence of randomized trials addressing essential issues of treatment and screening, my current personal recommendations would be as follows:

In a patient with incidentally discovered silent brain infarction, whether by CT or MRI, in the absence of known coronary or carotid disease or atrial fibrillation, I would advise intensive risk reduction strategies, including high-intensity statins, antithrombotic therapy and possibly low-dose colchicine, tight blood pressure and glycemic control, and lifestyle changes. Because these patients have an increased risk of carotid stenosis (odds ratio: 2.78)[9] a carotid duplex would be prudent.

In patients >60 years without known macrovascular disease or atrial fibrillation, who have multiple cardiovascular risk factors (eg, high Framingham Risk Scores correlate with increased silent brain infarctions prevalence and can be useful in patient selection),[10] I would discuss neuroimaging, preferably by MRI because the number needed to test to discover 1 silent brain infarction (the reciprocal of their estimated ~40% prevalence) is approximately 2.5, and positive finding can lead to significant changes in treatment and likely benefit the patient at high risk. Years of care of patients with potentially preventable dementia or stroke may well be more costly than neuroimaging screening judiciously offered to selective, high-risk populations. When silent brain infarction is discovered, increasing multipronged tackling of vascular risk factors seems a sensible and beneficial approach whose benefit is likely to exceed potential harm. Randomized trials of screening and treatment are ongoing or being planned.[3] But until solid evidence is available, active decisions on silent brain infarctions surveillance and treatment modifications must be not only individualized but also greatly dependent on the patient's point of view, readiness to bear the cost, and shared decision-making.

Ami Schattner, MD
Professor of Medicine, Hebrew University and Hadassah Medical School, Jerusalem, Israel

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