Poststroke Dementia

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Key Words

Poststroke dementia · Alzheimer's disease · Vascular dementia · White matter changes

Abstract

The association between stroke and dementia is frequent. The prevalence of poststroke dementia (PSD) ranges from 6 to 32%, depending on the population studied, the criteria used for the diagnosis of dementia, and the time interval between the stroke and the neuropsychological assessment. The risk of PSD is high immediately after stroke and remains higher than in controls in stroke patients nondemented 3 months after stroke. Not all cases of PSD are vascular in origin, with about one third of demented patients diagnosed as having Alzheimer's disease plus stroke. The pathophysiology of PSD is probably multifactorial, with an influence of vascular lesions, associated Alzheimer's lesions and white matter changes. The risk of dementia is higher in older patients and in patients with preexisting cognitive decline – no dementia, severe stroke, a history of stroke, white matter changes and cerebral atrophy. The influence of stroke location, vascular risk factors and silent infarcts remains to be determined. PSD adversely influences the outcome in stroke patients.

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The association between stroke and dementia is frequent. Poststroke dementia (PSD) has been an emerging field of research over the last decade, the term 'PSD' including any type of dementia occurring after a stroke, irrespective of its presumed cause.

Epidemiology of PSD

Prevalence

The prevalence of dementia in stroke survivors varies depending on the population studied, the criteria used for the diagnosis of dementia and the time interval between the stroke and the neuropsychological assessment. In population-based studies [1, 2], the prevalence of dementia in subjects with a history of stroke was about 30%, with a relative risk compared to stroke-free subjects ranging from 3.6 to 5.8. In hospitalized stroke patients ≥ 70 years the prevalence of dementia was 28% 1.5 years after stroke, with a relative risk of 4.7 compared to the controls, the relative risk being 4.8 in patients ≥ 80 years and 6.7 in patients < 80 years [3]. In cohorts of hospitalized stroke patients [4–18], the prevalence of PSD ranged from 6.2 to 32% (table 1). These discrepancies may be related to methodological differences [19]: the exclusion of aphasic patients or patients unable to undergo neuropsychological testing leads to a risk of underestimation of the prevalence of dementia [7, 20], while the lack of systematic research into cognitive disturbances existing prior to the

Table 1. Prevalence of PSD: literature data

Time interval after stroke	Prevalence %	Criteria used for the diagnosis of dementia	Population characteristics	Reference
7–10 days [4]	16.3	Clinician's opinion	Ischemic stroke Age ≥ 60 years	
1 month	32	Mattis Dementia Rating Scale score	First-ever stroke Age 60–80 years	Andersen et al. [6], 1996
3 months	5.9	NINDS-AIREN criteria	Stroke Exclusion of patients with previous functional deficit	Madureira et al. [13], 2001
	9.2	ICD-10 criteria	Ischemic stroke Exclusion of patients with previous TIA	Lin et al. [14], 2003
	13.6	NINDS-AIREN criteria	First-ever ischemic stroke	Censori et al. [7], 1996
	26.3, relative risk compared to controls = 9.2	DSM-III-R criteria	Ischemic stroke Age ≥ 60 years	Tatemichi et al. [5], 1992
	26.3	DSM-III-R criteria	Ischemic stroke Age ≥ 60 years	Desmond et al. [11], 2000
	22.1	DSM-IV criteria	Stroke Age ≥ 18 years	Barba et al. [10], 2000
	31.8	DSM-III criteria	Ischemic stroke Age 55–85 years	Pohjasvaara et al. [9], 1998
	15.5	DSM-IV criteria	Stroke Age ≥ 60 years	Tang et al. [16], 2004
	13.3	Clinical dementia rating scale score ≥ 1	Ischemic stroke associated with small vessel disease	Mok et al. [15], 2004
	27.2	DSM-IV criteria	Ischemic stroke Age ≥ 55 years	Zhou et al. [17], 2004
6 months	22.8	ICD-10 criteria	Stroke Age ≥ 40 years	Hénon et al. [12], 2001
	26	Mattis Dementia Rating Scale score	First-ever stroke Age 60–80 years	Andersen et al. [6], 1996
	8.5	DSM-IV criteria	First-ever ischemic stroke Age ≥ 40 years MMS ≥ 15 at the acute stage	Rasquin et al. [18], 2004
1 year	16.8	Proxy-informant interview based on ICD-10 criteria	Stroke	Inzitari et al. [8], 1998
	21.4	ICD-10 criteria	Stroke Age ≥ 40 years	Hénon et al. [12], 2001
	10	DSM-IV criteria	First-ever ischemic stroke Age ≥ 40 years MMS ≥ 15 at the acute stage	Rasquin et al. [18], 2004
1.5 years [3]	28	DSM-III-R criteria	Stroke Age ≥ 70 years	
2 years	21.6	ICD-10 criteria	Stroke Age ≥ 40 years	Hénon et al. [12], 2001
3 years	19.2	ICD-10 criteria	Stroke Age ≥ 40 years	Hénon et al. [12], 2001
TIA = Transient ischemic attack; MMS = Mini Mental State.

Fig. 1. Incidence of PSD at different time intervals after stroke onset.

stroke entails a risk of overestimation of the incidence of PSD, as prestroke dementia is frequent [21–25] and often undiagnosed [21].

Incidence

In a population-based study [26] conducted over a 25-year period, the cumulative incidence of PSD was 7% at 1 year, 10% at 3, 15% at 5, 23% at 10 years and increased to 48% at year 25. Compared to the stroke-free subjects, the relative risk of dementia was 8.8 one year after stroke, 4.5 at 3 years, 3.5 at 5, 2.5 at 10 years and decreased to 2.0 at the end of the follow-up period. In another study [27] conducted in initially nondemented subjects ≥ 75 years the relative risk of dementia after 3 years was 1.7 in patients with a history of stroke compared to the controls, the prior stroke being particularly potent when it had occurred within the preceding 3 months. In a more recent population-based study [28], a stroke doubled the risk of dementia uniformly over the 10-year study period, after a strict exclusion of patients with prestroke dementia. Only 1 community-based study [29] did not find strokes to be associated with a higher risk of dementia. However, this study was conducted in nonaphasic patients with a mild-to-moderate first-ever stroke and evaluated the risk of progressive dementia within 1 year.

Other studies were conducted in hospitalized stroke patients [12, 30–34]. Some of them [30–33] evaluated the incidence rate of PSD in patients not demented at months 3 or 6, the incident cases of dementia actually corresponding to delayed dementia occurring some months after the index stroke. The incidence rate of delayed PSD was 33.3% after 52 months of follow-up, with a relative risk of 5 compared to the controls [30]. Similar results, with a relative risk of 6 and a cumulative risk of dementia yielding almost 50% at year 9, were obtained in another study including the cohort of Tatemichi et al. [30] and a

second group of patients assembled later [31]. Other studies conducted in patients nondemented at month 3 found delayed PSD in 9% of patients ≥ 75 years within 1 year [33] and in 21% of stroke patients [32] within 4 years after stroke. The risk of delayed dementia was however much lower in the Lille stroke/dementia cohort, as only 6% of the patients who were not demented 6 months after stroke developed new onset dementia within 3 years [12]. The crude incidences of PSD in different studies are shown in figure 1.

From all these data we can conclude that the risk of PSD is high and that it is highest in the first months after stroke: about one fifth of stroke patients are demented in the first months following stroke, with consequences in terms of health care and cost evaluation. With respect to the risk of delayed PSD the data also suggest that stroke patients remain at a higher risk of dementia than stroke-free subjects do.

Risk Factors of PSD

Patients' Characteristics

Demographic Variables

Increasing age is clearly a risk factor of PSD [4–14, 17, 18, 26, 30–32, 35–37], the impact of stroke, however, being higher in younger patients [26, 28]. In most studies no influence of gender was observed [4, 5, 7, 9, 10–12, 14, 16, 17, 30–32, 35–37], while the data concerning the education level are controversial [4, 7, 9, 10–14, 16–18, 30, 31, 35–37].

Prestroke Functional Status and Cognitive Decline

The risk of PSD is higher in patients with a lower prestroke functional status [4, 6, 8, 10, 16] and prestroke cognitive decline/no dementia [10, 12, 15, 16].

Stroke Characteristics

Stroke Subtype

The risk and severity of cognitive disturbances occurring after a stroke do not seem to be influenced by the stroke type (ischemic or hemorrhagic) [10, 12, 13, 32].

Stroke Severity

The stroke severity influences the risk of PSD diagnosed soon after stroke. PSD diagnosed 3 months after stroke was more frequent in patients with a severe initial clinical deficit [7, 9–11, 14, 16, 35, 37]. The severity of the initial clinical deficit was also a predictor of PSD within 1 [8] and 3 years after stroke, with most cases of dementia occurring in the first months following stroke [12]. However, although the total volume of cerebral infarction is probably important, no threshold has been identified yet, as the volume of functional tissue loss may be more important [38]. The influence of stroke severity on delayed dementia is not obvious, and no relationship between stroke severity and risk of delayed dementia has been demonstrated yet [31, 32].

Stroke Location

The influence of the location of the vascular lesion remains to be determined. A role of the left hemisphere has been suggested [7–9, 14, 17, 35]. PSD was also found to be more frequent in patients with a hemispheric stroke compared to brainstem/posterior fossa lesions and in patients with a pooled anterior/posterior cerebral artery stroke compared to other locations [11]. On the other hand, many studies did not find any relationship between stroke location and risk of PSD [8, 10, 12, 13, 18, 26, 28, 31, 32]. In a population of stroke patients ≥ 75 years, none of the patterns of cerebrovascular disease highlighted as essential for the diagnosis of probable vascular dementia (VaD) by the NINDS AIREN criteria [39] was significantly different between stroke patients with or without PSD [40].

Only 1 study [37] has evaluated magnetic resonance imaging correlates of PSD, taking into account the volume, location and number of lesions. The conclusions suggest an influence of the lesions located in the left anterior corona radiata, part of the thalamocortical connection, and an influence of the total volume and number of infarcts. In this study larger volumes of right-sided infarcts (any infarct, frontal lobe and middle cerebral artery areas), and a larger volume (corona radiata, anterior centrum semiovale) and number (any infarct, deep posterior cerebral artery areas, pons, pallidum and anterior corona radiata) of infarcts on the left hemisphere were more fre-

quent in patients with PSD. The authors however conclude that dementia occurring after first-ever stroke is not solely due to a single stroke but a combination of infarct features (volume, location and number), the extent of white matter changes (WMC), medial temporal lobe atrophy (MTLA) and host factors.

Stroke Cause

No influence of the etiology of stroke determined according to the TOAST criteria [41] has been reported [7, 9, 11, 12, 14, 31]. However, in the Framingham study [28] strokes of atherothrombotic origin (including large-artery and lacunar infarcts and infarcts of unknown origin) doubled the risk of dementia compared to stroke-free subjects, while cardioembolic strokes did not increase the risk. Moreover, some data suggest that the risk of PSD could be lower in patients with a lacunar stroke than in those with a large arterial one [4, 11, 15, 18].

Vascular Risk Factors

The limited influence of well-established vascular risk factors such as hyperlipemia, arterial hypertension, tobacco and alcohol consumption on PSD is remarkable [4, 7–14, 16, 17, 26, 31, 32, 35]. However, the contribution of arterial hypertension to PSD might be masked by its significant contribution to strokes. The data concerning the influence of diabetes mellitus [4, 7–17, 26, 31, 32, 35] and atrial fibrillation [4, 7–12, 16, 17, 26, 31, 32, 35, 36] are controversial.

Previous Stroke and Stroke Recurrence

Previous stroke as well as stroke recurrence have been found to be associated with a higher risk of PSD in some [4, 8, 9, 11, 14, 15, 17, 26, 31, 35] but not all studies [12, 13, 16, 31, 32, 36]. However, this influence of previous or recurrent stroke might depend on the etiology of PSD: the risk is increased when PSD is vascular in origin, but not when it is degenerative in origin [35].

Hypoxic-Ischemic Disorders

Hypoxic-ischemic disorders were found to increase the risk of delayed dementia in stroke patients [31, 36]. Still, the association does not indicate causality and was not consistently found [12]. The category of hypoxic-ischemic disorders used is certainly too broad, including conditions that produce transient (seizure and syncope) and prolonged (heart failure and myocardial infarction) hypoxia. The association warrants further studies.

Radiological Data

Silent Infarcts

In the first study evaluating the relationship between PSD and silent infarcts [4], the frequency of dementia increased with the number and size of silent infarcts, whereas another study did not find any relationship between silent infarcts and PSD [34]. Nevertheless, in this study, despite a long follow-up, the small number of subjects may have led to a lack of power of the statistical analysis. The presence of silent infarcts on CT performed in the acute phase of the stroke was actually found to be an independent predictor of PSD [12, 37].

Cerebral Atrophy

Cerebral atrophy is a predictor of PSD [4, 12, 16, 32, 37, 42]. MTLA is more frequent in stroke patients with preexisting dementia [22] but also exists in nondemented ones and is associated with a higher risk [37, 40, 43]. Stroke patients with MTLA could have preclinical Alzheimer's disease (AD), clinically revealed by stroke, even if MTLA does not seem to be specific to AD and is also observed in VaD [44–46]. It remains to be determined to what extent the presence of MTLA is a risk factor for delayed PSD.

White Matter Changes

WMC probably play a role in the development of PSD [4, 6, 12, 16, 37]. The major confounding factors may, however, be the presence of cerebral atrophy and lacunar infarcts, which are associated with a higher frequency of both WMC and dementia and probably share a common pathogenesis with WMC.

Functional Neuroimaging

To our knowledge, there is no study with functional neuroimaging techniques, such as single-photon emission CT, positron emission tomography, functional magnetic resonance imaging or spectroscopy, aiming to identify predictors of PSD in consecutive stroke patients.

Etiology of PSD

Only few data concerning the etiology of PSD are available. They almost all suggest that PSD is not always vascular in origin.

In the Rochester study [26], 1% of patients with PSD were diagnosed as having AD. The incidence of AD within 1 year was 2.6-fold higher in the stroke patients compared to the controls, followed by a 50% annual excess of

AD in the stroke cohort compared to the community for 25 years of observation. In another population-based study [2], about half of the cases were diagnosed as probable VaD because the dementia occurred immediately after stroke, while about half of the cases were considered as possible VaD, since the dementia onset was insidious and occurred more than 4 months after the stroke onset. In the Framingham study [28], the majority of stroke subjects developed either VaD (51%) or mixed dementia (AD with VaD, 37%).

Most available data concerning the etiology of PSD have been obtained in stroke cohorts, with neuropsychological evaluation performed within the first 3 months after stroke. Of the patients demented 3 months after stroke [5, 9, 11, 35] 19–39% were diagnosed as having AD + stroke because cognitive disturbances had been present prior to stroke, the remainder in most cases being diagnosed as having dementia directly related to vascular disease. However, in these studies [5, 9, 11, 35] a bias due to the absence of strict exclusion criteria for patients with undiagnosed prestroke dementia is possible. In the study of Barba et al. [10] patients with prestroke dementia were diagnosed using a standardized methodology, but the authors did not separate the patients with pre- and post-stroke dementia in their analysis. They found 71% of patients with PSD to have probable VaD and 29% to have possible VaD, including 16% with mild-to-moderate mental impairment of insidious onset and a progressive course (probable AD) before the stroke and 9% who showed a slow progression of cognitive decline after the stroke. Nevertheless, even after the exclusion of the patients with prestroke dementia using a standardized methodology [12], about one third of the patients with PSD were diagnosed as having AD, always at the month 6 visit, while two thirds received the diagnosis of probable or possible VaD.

Only 2 studies, both conducted in Asian countries [14, 16], did not confirm this high proportion of degenerative dementia in patients with PSD. However, in the first one [14] the population studied was about 10 years younger than the population evaluated in previous studies; in the second one [16] the diagnosis of VaD was based on DSM IV criteria, which are less specific than others [47].

From all these data we can conclude that PSD is not always vascular in origin, even if it occurs immediately after stroke. Only few data [12, 26, 32] concerning delayed dementia are available, but they also suggest that delayed PSD is probably of vascular origin in some cases and of degenerative origin in others: 63% of patients with delayed PSD were diagnosed as having probable VaD and 37% as having possible AD [32].

Mechanisms of PSD

PSD patients do not constitute a homogeneous group.

Prestroke Dementia

Prestroke dementia is frequent [21–25] and often undiagnosed [21, 22]. In the absence of a systematic evaluation of prestroke cognitive status, many cases of PSD are certainly prestroke dementias. It follows that many of these could be degenerative in origin [21].

'Pure' VaD

Vascular lesions play a role in the development of PSD, and PSD is probably due to stroke alone under the following circumstances: (1) in young stroke patients who become demented after 1 or several strokes, (2) when the clinician has a high level of certainty that the cognitive functioning of the patient was normal before stroke, impaired immediately after and will not worsen over time or even slightly improve, (3) when the lesions are located in strategic areas and (4) when a specific vascular condition known to cause dementia (such as cerebral autosomal dominant angiopathy with subcortical infarcts and leukoencephalopathy) is proven by pathological data or a specific marker. It is important to notice that 'strategic' locations have been described in single cases or in small series [48–51]. Nevertheless, in case reports with first generations of CT scans, another vascular lesion of the brain cannot be excluded and may interfere with the neuropsychological profile [52]. Moreover, in elderly patients without follow-up the contribution of Alzheimer lesions cannot be excluded [53–55]. The concept of strategic stroke should therefore be revised with modern imaging techniques and a longer follow-up.

The Multifactorial Origin of PSD

Many cases of PSD are probably the consequence of the cumulative effect of vascular lesions, AD and WMC. The links between cerebrovascular disease and AD are close [54]. Elderly subjects without a history of stroke but with cognitive decline have a high risk of stroke [56]. The risk of AD is increased, with an earlier age at the onset of dementia, in subjects with a history of stroke, with a higher risk for those who also have vascular risk factors [57]. Alzheimer and vascular lesions of the brain are frequently associated at autopsy [58, 59]. Patients with AD have some degree of vascular changes [60, 61], which may cause cerebral hemorrhages or infarcts, lacunas and WMC. Shared risk factors of the 2 clinical entities may

also be responsible for their co-occurrence. Besides advancing age, 1 of them might be the allele $\epsilon 4$ of the apolipoprotein E gene [62], which is associated with an increased risk of cerebral infarct [63], with a greater progression of cognitive decline in old stroke patients with cognitive decline/no dementia [64] and perhaps also with an increased risk of AD [65]. However, no difference was found for the frequency of apolipoprotein E $\epsilon 4$ alleles and apolipoprotein E gene promoter polymorphisms between patients with and without PSD 3 months after stroke [66]. Arterial hypertension, smoking and increased intima-media thickness in the common carotid artery are also risk factors common to vascular diseases and AD [67].

WMC are related to strokes. They are frequent in VaD and are also found in AD, especially with late onset. In healthy elderly subjects they are associated with subtle neuropsychological [68, 69] and behavioral changes [70]. WMC may contribute to dementia in stroke patients because they indicate an increased risk of stroke recurrence [71], and they lead to a subtle cognitive decline with the possible consequences of stroke lesions and even associated Alzheimer pathology [72]. Even if vascular lesion, Alzheimer pathology or WMC do not lead to dementia by themselves, their cumulative effect may reach the threshold of lesions required to produce dementia [54]. If a stroke, WMC or both occur in a patient with asymptomatic AD, the period of preclinical AD may be shortened. In the nun study, among patients who met neuropathological criteria for AD, those with brain infarcts had poorer cognitive functions and a higher prevalence of dementia than those without infarcts, while among patients who did not meet the neuropathological criteria for AD, brain infarcts were only weakly associated with poor cognitive functions and dementia [53], suggesting that stroke lesions may play a role in determining the presence and severity of the clinical symptoms of AD. This result is supported by another study [73], conducted on older catholic clergy, which found AD pathology and macroscopic cerebral infarctions to contribute additively to the likelihood of dementia, however, without evidence of an interaction between both. In patients included in the dementia substudy of Systolic Hypertension in Europe a beneficial effect of antihypertensive therapy on the risk of cognitive decline and of AD was shown [74]. This effect may result from the reduced incidence of infarcts by lowering of the blood pressure, which prevents the anticipation of the clinical expression of AD [75]. Moreover, it has been shown that previous cognitive decline – no dementia is a risk factor for PSD, suggesting that some

diagnoses of PSD could be AD, subclinical before stroke, but revealed by stroke.

Influence of PSD on Stroke Patients' Prognosis

Functional Outcome

The few data published suggest that patients with PSD are functionally impaired and dependent in daily living activities [4, 5, 10, 14].

Mortality

Patients with dementia have a higher mortality rate, independently of the effects of age and comorbidities [76, 77]. The mortality rate is also increased in patients with PSD [42, 78–81], the relative risk of death ranging from 2.4 to 6.3. Many mechanisms may underlie this increased mortality rate. Dementia could be associated with a more severe vascular disease and a higher risk of complications [42], but the causes of death did not differ between demented and nondemented patients [79, 80], even though the number of vascular deaths tended to be higher in the group of demented patients [80] and was highest in the group with PSD considered as vascular in origin [79]. Another possibility is that dementia could be a worsening factor when an intercurrent disease occurs, either because of a decreased capacity to respond to aggressions or because demented patients receive less aggressive treatment [82–84]. Moreover, demented patients may be less compliant with the treatment regimens that are actually prescribed.

Stroke Recurrence

The data concerning the influence of PSD on the risk of stroke recurrence are controversial. Dementia diagnosed 3 months after stroke was associated with an increased risk of stroke recurrence of about 3 [85], suggesting that dementia may be a surrogate marker for multiple vascular risk factors that might augment the risk of recurrence. On the other hand, a less intensive management of stroke patients with dementia as well as their lack of compliance may also contribute to the increased risk of recurrence [86]. An argument in favor of this hypothesis is that the risk of stroke recurrence was not increased in patients with PSD when no difference in the treatment for stroke prophylaxis was observed between demented and nondemented patients [12]. Moreover, the presence of WMC could be a confounding factor, WMC being strongly associated with stroke recurrence [12].

Treatments of PSD

The management of PSD focuses on secondary prevention treatment with control of cerebrovascular risk factors. A better control could diminish the risk of cognitive decline by reducing the risk of stroke recurrence with an indirect effect on the clinical expression of the degenerative processes. However, the results of controlled hypertension trials are controversial [74, 87–90].

Another therapeutic approach is the cholinergic strategy. Vascular lesions may produce a cholinergic dysfunction due to ischemic damage of basal forebrain neurons or their projections, similar to that seen in AD [91]. In studies on cholinesterase inhibitors in patients with pure VaD, the treatment showed to be effective in improving cognition and preventing functional deterioration [92–95]. In addition, cholinergic agents should be beneficial in the third of PSD patients considered as having AD associated with stroke.

Discussion

Hospital- and community-based studies provide similar findings: a stroke doubles the risk of dementia, the risk is highest within the first months after stroke, as almost 1 patient out of 5 is demented, and the risk of delayed dementia (including AD) is also doubled after stroke. All published studies suggest that PSD adversely influences the vital and probably functional outcome. The following factors have been identified as associated with a higher risk of PSD: increasing age, prestroke loss of autonomy and cognitive decline/no dementia, diabetes mellitus, atrial fibrillation, and, from a radiological point of view, silent infarcts, global cerebral atrophy, MTLA and WMC. Previous stroke and stroke recurrence are also related to a higher risk of PSD. No clear conclusion concerning the influence of the stroke location and size can be drawn from the published studies. This is probably mainly due to the fact that PSD is not a disease but a syndrome, whose origin is in many cases multifactorial, with the intervention of stroke characteristics but also of WMC and underlying degenerative diseases. Indeed, about one third of PSD diagnoses are AD, and only two thirds of patients are diagnosed as having VaD (even in these patients an underlying degenerative disease often cannot be excluded). From that perspective the concept of PSD, supposed to help understand the pathophysiology of VaD, has not been very useful. If the aim is to better comprehend the mechanism underlying VaD, further studies are needed,

carefully excluding patients with prestroke cognitive decline and poststroke AD. On the other hand, the concept of PSD has been valuable for patients who are followed up after a stroke, before the diagnostic workup allows a classification into vascular, degenerative and mixed dementia. The fact has been pointed out that dementia is very frequent in stroke patients, sometimes even present but undiagnosed before stroke. The concept of PSD has led to conduct trials in stroke patients whose secondary

endpoint was cognitive outcome [89, 91] and could also be useful to focus on cognitive impairment rather than dementia because the former takes into account all the cognitive consequences of strokes, even if the criteria for dementia are not present. We should bear in mind that the true cognitive burden of strokes is underestimated, cognitive impairment without dementia being 3 times more frequent in patients who had a stroke than in stroke-free controls [3].

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