

Insulin Resistance in Cognitive Impairment

The InCHIANTI Study

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Objective: To test the association between cognitive impairment, with and without subcortical features, and insulin resistance in an elderly community-dwelling population.

Design: Cross-sectional wave of an epidemiologic longitudinal study (InCHIANTI).

Participants: A total of 523 people, aged 70 to 90 years without diabetes mellitus or hyperglycemia, from the InCHIANTI cohort were included in the study. A total of 119 individuals had cognitive impairment (Mini-Mental State Examination [MMSE] score <25), 21 of whom had both cognitive impairment and subcortical features (CI/SF+ group). Control groups contained 23 individuals with a history of stroke and 381 individuals with no cognitive impairment (no CI group, MMSE score \geq 25). Indicators of insulin resistance were the fasting plasma insulin level, insulin resistance index (Homeostasis Model Assessment of Insulin Resistance [HOMA-IR]), and insulin sensitivity index (Quantitative Insulin Sensitivity Check Index [QUICKI]).

Results: The insulin resistance profile of patients in the CI/SF+ group was similar to that of individuals who had

experienced stroke, whereas the profile of individuals with cognitive impairment without subcortical features (CI/SF- group) was similar to that of individuals in the no CI group. Patients in the CI/SF- group showed insulin resistance comparable to individuals in the no CI group (age-adjusted $P=.27$, $.19$, and $.64$, respectively, for difference in fasting blood insulin level, HOMA-IR, and QUICKI in linear regression models) and lower than patients with stroke (age-adjusted $P=.01$, $.02$, and $.07$, respectively). On the contrary, patients in the CI/SF+ group had insulin resistance and sensitivity values similar to those of the stroke group (age-adjusted $P=.80$, $.84$, and $.75$, respectively, for difference in fasting blood insulin level, HOMA-IR, and QUICKI) but significantly different from those in the no CI group (age-adjusted $P=.01$, $.03$, and $.02$, respectively).

Conclusions: Cognitive impairment with but not without subcortical features is associated with biochemical and clinical features of insulin resistance syndrome. In epidemiologic populations, insulin resistance might contribute to cognitive impairment through a vascular mechanism.

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ALZHEIMER DISEASE (AD) IS a primary degenerative dementia. A growing body of evidence, however, suggests that microvascular lesions might represent a co-occurring factor that both determines the onset¹ and influences the clinical expression of AD.² This observation is supported by the recent description of several risk factors for AD, which are also well-known risk factors for cerebrovascular disease, including hypertension,^{3,4} hypercholesterolemia,⁵ coronary heart disease,⁶ atrial fibrillation,⁷ generalized atherosclerosis,⁸ and diabetes mellitus.⁹ Type 2 diabetes mellitus is particularly interesting, especially in the early stage, characterized by progressing insulin peripheral resistance and high fasting blood insulin levels, but normal fasting blood glucose levels. This

condition is almost invariably associated with cardiovascular, metabolic, and endocrine disorders (such as systemic hypertension, obesity, elevated plasma triglycerides and total cholesterol levels, and

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decreased high-density lipoprotein cholesterol [HDL-C] levels), constituting the insulin resistance (IR) syndrome (also called syndrome X or the metabolic syndrome),

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which is a strong risk factor for ischemic cardiac events¹⁰ and stroke.¹⁰

Epidemiologic observations have led us to hypothesize that hyperinsulinemia can

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cause cognitive impairment and dementia, because the IR syndrome is more frequently found in patients with dementia than in healthy individuals, and cognitively intact persons with IR syndrome are more prone to develop dementia.¹¹ The pathogenic mechanism of this association is still unclear, but some hypotheses have been proposed that involve the alteration of amyloid β -peptide (A β) metabolism with increased amyloid deposition¹² and increased phosphorylation of the tau protein.¹³ However, hypothetically hyperinsulinemia increases the risk of cognitive impairment through microvascular abnormalities.¹¹ Brain subcortical small-vessel lesions are unlikely to cause cognitive impairment but rather cause a syndrome characterized by neurologic and neuropsychological features, such as parkinsonism, gait disorders, dysexecutive syndrome, and relative sparing of memory.² If cognitive impairment associated with IR is due to microvascular lesions, individuals with cognitive impairment and no subcortical features, in whom a neurodegenerative cause is likely, should have a normal IR profile, whereas those with cognitive impairment and subcortical features should have a profile more similar to that of patients with cerebrovascular disease. The aim of this study was to compare the IR profile of patients who had cognitive impairment with and without subcortical vascular features with that of individuals with a history of stroke and healthy individuals (no cognitive impairment and no history of stroke) living in the community.

METHODS

STUDY PARTICIPANTS

These data are from InCHIANTI, a population-based epidemiologic study conducted in the Chianti geographic area (Tuscany, Italy) and aimed at studying factors that affect mobility in older persons. The methodologic details of the study have been described elsewhere.¹⁴ Briefly, in August 1998, 1260 persons 65 years or older were randomly selected from the population registry of Greve in Chianti (a rural area; 11 709 inhabitants; 19.3% \geq 65 years) and Bagno a Ripoli (an Antella village a few kilometers from Florence; 4704 inhabitants; 20.3% \geq 65 years). The participation rate was 91.6% (1154/1260).

For the purpose of the present study, those 774 individuals between 70 and 90 years of age were considered. Younger and older individuals were excluded because the epidemiology and the clinical picture of dementias in the extreme ages (young and oldest-old people) are different.

The InCHIANTI study protocol was approved by the Italian National Research Center on Aging institutional review board. All participants were given extensive information about the project and signed an informed participation consent. For participants who were unable to provide a full consent, for cognitive or sensory impairment, we obtained an assent and a surrogate consent from a proxy.

COGNITIVE ASSESSMENT

Global cognitive performance was assessed with the Mini-Mental State Examination (MMSE).¹⁵ The performance on the back-7 and backward spelling items of the MMSE (the highest score on either task) was considered a proxy of executive function performance. The back-7 and backward spelling tests tap attention, load heavily on working memory, and have been found impaired in patients with dysexecutive syndrome.¹⁶

DIABETES AND INDICATORS OF IR

Diabetes mellitus was defined as at least 1 of the following: a physician's diagnosis in the medical history, current treatment with insulin or oral hypoglycemic drugs, self-report of diabetes and measured fasting blood glucose level of 126 mg/dL or higher (\geq 6.99 mmol/L), and measured fasting blood glucose level of 200 mg/dL or higher (\geq 11.1 mmol/L).

Indicators of insulin resistance were as follows: (1) fasting blood insulin level, determined by a commercially available radioimmunoassay kit (coefficient of variation, mean \pm SD, 3.2% \pm 0.3%; cross-reactivity with 0.3% proinsulin; Sorin Biomedical, Milan, Italy)¹⁷; (2) IR index, estimated using the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR)¹⁸. IR = [fasting glucose level (millimoles per liter)] \times [fasting insulin level (microunits per milliliter)]/22.5; and (3) insulin sensitivity index, computed with the Quantitative Insulin Sensitivity Check Index (QUICKI)¹⁹: insulin sensitivity = 1/[log fasting insulin level (microunits per milliliter)] + [log fasting glucose level (milligrams per deciliter)].

FEATURES CHARACTERIZING IR SYNDROME AND VASCULAR RISK FACTORS

The IR syndrome, according to the definition of metabolic syndrome of the National Cholesterol Education Program,²⁰ includes the following elements: (1) current use of 1 or more antihypertensive drugs (diuretics, β -blockers, calcium antagonists, angiotensin-converting enzyme inhibitors) and/or a systolic blood pressure of 130 mm Hg or higher and/or diastolic blood pressure of 85 mm Hg or higher on physical examination; (2) a serum triglyceride level higher than 150 mg/dL (1.70 mmol/L); (3) an HDL-C level lower than 40 mg/dL (1.04 mmol/L) in males or lower than 50 mg/dL (1.30 mmol/L) in females; (4) abdominal obesity, defined as waist circumference greater than 102 cm in males or greater than 88 cm in females; and (5) a fasting blood glucose level higher than 120 mg/dL (6.66 mmol/L). In addition, we considered high levels of insulinemia, defined as values of fasting blood insulin in the highest quintile of the distribution in this population.

DEFINITION OF THE STUDY GROUPS

Of the 774 participants aged 70 to 90 years, 251 were consecutively excluded because they had diabetes (n=78) or high fasting blood glucose values ($>$ 125 mg/dL [$>$ 6.94 mmol/L]; n=17), data on diabetes or blood glucose (n=87) were missing, data on MMSE scores (n=40) or insulin (n=19) were missing, or they were affected by Parkinson disease (n=6). To avoid possible mistakes in the level of fasting blood insulin, individuals with extremely high values (over 3 SDs; n=4) were also excluded from the analysis.

Of the remaining 523 participants, 23 (4%) reported a history of stroke and constituted the control group (stroke group). A total of 381 (73%) of the participants without stroke did not show a cognitive impairment (CI; MMSE score \geq 25); these individuals constituted the second control group (no CI group). Individuals who scored 24 or less on the MMSE (119, 23%) were considered to have cognitive impairment and were placed in 2 subgroups. Twenty-one were defined as having cognitive impairment with subcortical features (CI/SF+ group). Individuals in this group recalled at least 2 (when the total MMSE score was 19 to 24) or 1 (when the MMSE score was \leq 18) bisyllabic words on the MMSE and showed at least 2 of 3 of the following features: plastic rigidity (parkinsonism) in at least 2 of 5 areas (neck, upper and lower limbs); small-step gait or parkinsonian gait; and dysexecutive features, defined as scoring 3

Table 1. Sociodemographic and Clinical Features of the Study Groups

Feature	No CI (n = 381)	CI/SF- (n = 98)	CI/SF+ (n = 21)	Stroke (n = 23)	P Value*
Age, mean ± SD, y	76 ± 5	80 ± 5	80 ± 5	78 ± 5	<.001
Female, No. (%)	215 (56)	60 (61)	16 (76)	9 (39)	.08
MMSE score, mean ± SD	27 ± 2	21 ± 5	22 ± 3	22 ± 8	<.001

Abbreviations: CI/SF-, cognitive impairment without subcortical features; CI/SF+, cognitive impairment with subcortical features; MMSE, Mini-Mental State Examination; no CI, no cognitive impairment.

*P represents statistical significance with analysis of variance (for continuous variables) or χ^2 test (for categorical variables).

or less of 5 on both the back-7 and backward spelling items of the MMSE. The other group with cognitive impairment was labeled CI/SF- (n=98).

DATA MANAGEMENT AND STATISTICAL ANALYSIS

The significance of differences in continuous variables among and between groups was assessed with the 1-way analysis of variance and *t* test for independent samples, respectively. Differences in proportions were assessed with the χ^2 test. The significance of the difference between 2 groups for continuous variables (insulin, HOMA-IR, and QUICKI) was tested in linear regression models in which the variable of interest was the dependent variable and group and age were the independent variables. The significance of the difference in the prevalence of the features of IR syndrome between the 2 groups was tested in multinomial logistic models in which the 3-level variable of interest (no features, 1-2 features, and ≥ 3 features) was the dependent variable and group and age were the independent variables.

RESULTS

Participants with cognitive impairment both with and without subcortical features were significantly older than those without cognitive impairment and those with stroke. As expected, the MMSE score was higher in the no CI group, whereas it was similar in the other 3 groups (**Table 1**).

The distribution of fasting blood insulin, HOMA-IR, and QUICKI values are shown in **Figure 1**. The 2 cognitive impairment groups were substantially different, with the CI/SF+ group showing significantly more marked insulin resistance than the CI/SF- group (age-adjusted $P = .001$, $.001$, and $.005$ for insulin, HOMA, and QUICKI, respectively). The CI/SF- group had less IR than the no CI group, although the difference was not statistically significant ($P = .27$, $.19$, and $.64$, respectively). The CI/SF- group also had significantly lower IR than the stroke group (age-adjusted $P = .01$, $.02$, and $.07$ for fasting blood insulin, HOMA-IR, and QUICKI, respectively). On the contrary, the CI/SF+ group had IR and sensitivity values similar to those of the stroke group ($P = .80$, $.84$, and $.75$, respectively, for insulin, HOMA-IR, and QUICKI), but insulin and IR were significantly higher (age-adjusted $P = .01$ and $.03$ for fasting blood insulin and HOMA-IR) and insulin sensitivity was significantly lower (age-adjusted $P = .02$ for QUICKI) than those of the no CI group.

Table 2 gives the cerebrovascular risk factors and traits characteristic of the IR syndrome in the 4 study groups.

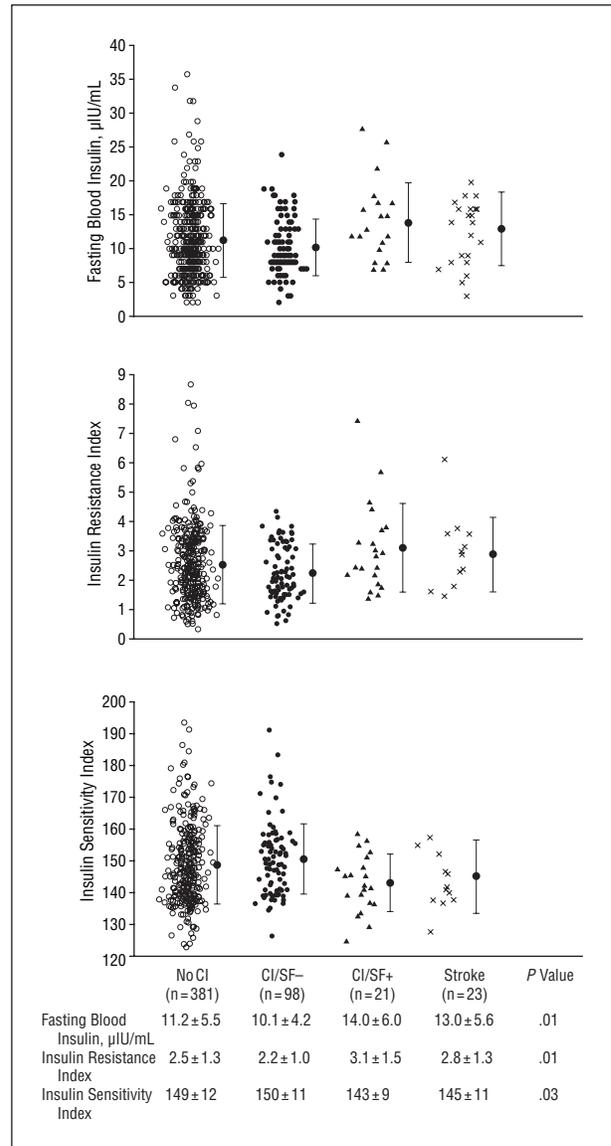


Figure 1. Distribution of insulin, insulin resistance (Homeostasis Model Assessment of Insulin Resistance), and insulin sensitivity (Quantitative Insulin Sensitivity Check Index) mean ± SD values in the study groups. CI/SF- indicates cognitive impairment without subcortical features; CI/SF+, cognitive impairment with subcortical features; and no CI, no cognitive impairment. Error bars indicate standard deviation; open circles, the no CI group; solid circles, the CI/SF- group; triangles, the CI/SF+ group; and X's, the stroke group.

The CI/SF+ group tended to have more unfavorable values of blood pressure and blood lipid levels than the other groups, but HDL-C and triglyceride levels were signifi-

Table 2. Cerebrovascular Risk Factors and Prevalence of Features of the Insulin Resistance Syndrome in the Study Groups

Variable	No CI (n = 381)	CI/SF- (n = 98)	CI/SF+ (n = 21)	Stroke (n = 23)	P Value*
Cerebrovascular risk factors, mean ± SD					
Fasting blood glucose, mg/dL	89 ± 11	87 ± 11	87 ± 10	88 ± 9	.30
Systolic blood pressure, mm Hg	151 ± 19	153 ± 19	155 ± 19	152 ± 17	.47
Diastolic blood pressure, mm Hg	84 ± 9	84 ± 6	86 ± 7	82 ± 8	.47
HDL-C, mg/dL	57 ± 15	57 ± 15	51 ± 15	48 ± 10	.02
Triglycerides, mg/dL	120 ± 54	117 ± 69	168 ± 101	149 ± 70	.001
Waist circumference, cm†	92.7 ± 10.5	88.8 ± 10.0	92.3 ± 9.7	94.2 ± 13.0	.01
Features that characterize insulin resistance syndrome, No. (%)					
Hyperinsulinemia	74 (19)	14 (14)	7 (33)	8 (35)	.05
Hyperglycemia	19 (5)	7 (7)	0	0	.35
Hypertension	353 (93)	93 (95)	20 (95)	22 (96)	.80
Low HDL-C level	83 (22)	21 (21)	9 (43)	5 (22)	.16
High triglycerides level	78 (21)	20 (20)	10 (48)	8 (35)	.01
Abdominal obesity (increased waist circumference)	149 (40)	30 (33)	12 (60)	7 (37)	.16

Abbreviations: CI/SF-, cognitive impairment without subcortical features; CI/SF+, cognitive impairment with subcortical features; HDL-C, high-density lipoprotein cholesterol; no CI, no cognitive impairment.

SI conversion factors: To convert glucose to millimoles per liter, multiply by 0.0555; cholesterol to millimoles per liter, multiply by 0.0259; triglycerides to millimoles per liter, multiply by 0.0113.

*P represents statistical significance with analysis of variance (for continuous variables) or χ^2 test (for categorical variables).

†Data are not available for 19 individuals: 7, 7, 1, and 4 in the no CI, CI/SF-, CI/SF+, and stroke groups, respectively.

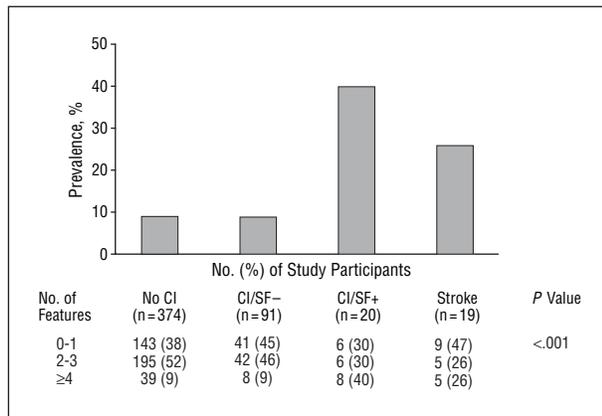


Figure 2. Prevalence of features of the insulin resistance syndrome (hyperinsulinemia, hyperglycemia, hypertension, low high-density lipoprotein cholesterol level, high triglyceride level, and abdominal obesity). Bars denote the proportion with 4 or more features. CI/SF- indicates cognitive impairment without subcortical features; CI/SF+, cognitive impairment with subcortical features; and no CI, no cognitive impairment.

cantly different. Of the 6 features characteristic of the IR syndrome, 2 (hyperinsulinemia and high triglyceride level) were significantly more prevalent in the CI/SF+ group; another 2 features (low HDL-C level and abdominal obesity) were more prevalent in the CI/SF+ group, but this difference did not reach statistical significance ($P = .16$). As shown in **Figure 2**, the distribution of the number of features was also different among the study groups, and 2 different trends resulted: 4 or more features of the IR syndrome were present in less than 10% of the participants in the no CI and CI/SF- groups, in 40% of those in the CI/SF+ group, and in 26% of those in the stroke group. In age-adjusted models, the CI/SF- group was similar to the no CI group ($P = .63$) but significantly different from the CI/SF+ group ($P = .001$) and nearly significantly different from the stroke group ($P = .07$). On the contrary, the CI/SF+ group was similar to the stroke group

($P = .53$) and different from the no CI group ($P = .001$). Since the prevalence of participants with blood pressure reaching 130/80 mm Hg was very high (more than 90% in all groups), analysis was rerun with a looser cutoff for high blood pressure (systolic ≥ 160 mm Hg or diastolic ≥ 90 mm Hg). The prevalence of hypertension in the 4 groups was 62%, 70%, 67%, and 70% in the no CI, CI/SF-, CI/SF+, and stroke groups, respectively. The association of subcortical features with the IR syndrome was unchanged.

COMMENT

Our data indicate that cognitive impairment with clinical features indicative of subcortical vascular damage is associated with IR in individuals with no diabetes. This finding suggests that in epidemiologic populations, IR might contribute to cognitive impairment through a vascular mechanism.

The association of IR syndrome and dementia has been observed in clinical²¹ and epidemiologic¹¹ studies. Razay and Wilcock²¹ found that compared with sex-matched controls, patients affected by AD had higher fasting plasma insulin levels, although the difference reached statistical significance in women but not in men. In a population of 980 patients 69 to 79 years old, Kuusisto et al¹¹ reported that fasting insulin values were significantly higher in 46 patients with AD than in persons without dementia. The authors hypothesized that hyperinsulinemia might interfere with the metabolism of A β and tau proteins, making the brain more prone to AD lesions.

Current information from neurobiological and neuropathologic studies indicates that insulin has important functions in the brain,¹³ where it is both synthesized and transported to the cerebrospinal fluid.²² The presence of insulin-sensitive glucose transporters in the

hippocampus²³ provides a convincing explanation for the direct effects of insulin on brain glucose metabolism,²⁴ against the traditional notion that the brain is not an insulin-sensitive organ. As a consequence, patients with IR require higher levels of insulin not only in peripheral tissues but also for normal brain activity.²⁵ Chronically high levels of insulin, however, might play a role in the pathogenesis of neuropathologic lesions of AD. In fact, high insulin levels can lower soluble amyloid precursor protein levels in the plasma and increase A β 42 levels in the cerebrospinal fluid.¹²

The mechanisms that have been proposed to explain the possible pathogenetic link between IR and AD are focused on hyperinsulinemia, the principal but not the only feature of the IR syndrome. One or more cardiovascular, metabolic, and endocrinologic features, representing risk factors for macrovascular and microvascular disease, are almost invariably associated with hyperinsulinemia in the IR syndrome²⁶ and can increase the risk of dementia.²⁷ Therefore, a role of the atherosclerosis that characterizes the IR syndrome in determining dementia²⁸ cannot be excluded. Our data could lead to the hypothesis that the IR syndrome might cause cognitive impairment in at least 2 ways. In vitro (ie, when only the effects of insulin are taken into account), hyperinsulinemia interferes with the amyloid precursor protein and A β metabolism, thus promoting the onset of AD-specific neuropathologic lesions. In vivo, the IR syndrome causes and sustains microvascular damage, not only with hyperinsulinemia but mainly by means of the other factors of the IR syndrome.

Some limitations of the study must be underlined. First, neuroimaging was not available for these participants. Brain magnetic resonance imaging or computed tomography could provide direct evidence of subcortical lacunes, leukoaraiosis, or white matter lesions. However, although the relationship between leukoaraiosis and clinical features such as parkinsonism and subcortical vascular dementia is clear, an exact correlation has not been established between the severity of subcortical vascular disease, as visually rated by computed tomography or magnetic resonance imaging, and onset or severity of clinical symptoms. Therefore, neuroimaging could be useful to ascertain the presence of subcortical vascular disease but not to demonstrate that this is causally linked to subcortical features. Second, lacking both neuroimaging and a detailed neuropsychiatric history, some persons in the CI/SF+ group might have dementia with Lewy bodies.²⁹ This is the second most prevalent degenerative dementia in elderly patients³⁰ and is characterized by symptoms common with subcortical vascular dementia: cognitive impairment, parkinsonism, and poor performance on executive functions tests. Other symptoms more specific to dementia with Lewy bodies, such as well-formed and detailed visual hallucinations, could help in the differential diagnosis, but this information is not available in the InCHIANTI data set. However, there is no difference among groups regarding the use of neuroleptics (2%, 6%, 5%, and 0% in the no CI, CI/SF-, CI/SF+, and stroke groups, respectively), suggesting that hallucinations and other psychotic symptoms might have a similar prevalence among groups. The possible association

of dementia with Lewy bodies with IR needs to be assessed in future studies. Third, our data are based on a cross-sectional study. Longitudinal data would allow investigation of the effect of hyperinsulinemia and IR on the onset of dementia. Finally, we do not perform an insulin clamp, the test that directly evaluates the IR. The 2 indexes based on the fasting blood insulin and glucose levels only allow estimation of both IR and sensitivity.

Data from this study could have some clinical implication for the elderly population. In particular, treatment of IR before the onset of overt diabetes mellitus might be effective in preventing not only diabetes but also the proportion of dementias associated with subcortical vascular disease, which present with subcortical features.

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