Cognitive function predicts first-time stroke and heart disease

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Abstract—*Objective:* To investigate whether impaired cognitive function is an early manifestation of vascular injury in the brain and therefore predicts risk of subsequent cardiovascular disease. *Methods:* The study population consisted of 12,096 middle-aged participants in the Atherosclerosis Risk in Communities (ARIC) Study who had no history of stroke or coronary heart disease (CHD) at the time of cognitive testing. Cognitive function was measured using the Digit-Symbol Substitution Test (DSST), the Word Fluency Test, and the Delayed Word Recall Test. Cognitive test scores were adjusted for demographic factors and then evaluated as predictors of incident cardiovascular events using Cox proportional hazards analysis. *Results:* Over a median follow-up period of 6.4 years, there were 516 incident cardiovascular events (292 myocardial infarctions, 50 CHD deaths, and 174 strokes), resulting in an average annual incidence rate of 0.7%. Lower adjusted scores on each cognitive test predicted a greater risk of incident cardiovascular events after controlling for established vascular risk factors (highest vs lowest quartile DSST, adjusted hazard ratio 1.56, 95% CI 1.23 to 1.97, p for linear trend by quartile < 0.001). The magnitude of the association was comparable with other commonly used predictors of vascular risk such as left ventricular hypertrophy on EKG and high-density lipoprotein cholesterol level of <35 mg/dL. *Conclusion:* Cognitive test scores below demographic norms predict incident cardiovascular disease in middle-aged subjects independently of established vascular risk factors.

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Identification of new risk factors for cardiovascular disease has the potential to improve prevention efforts and create more efficient strategies for targeting therapy. Markers of vascular disease burden have particular importance in this regard as they may provide information not only about exposure to known risk factors but also about an individual's underlying susceptibility to them.

Recent studies have demonstrated that impaired cognitive function may be an early and sensitive indicator of vascular injury in the brain. Vascular risk factors at midlife, such as hypertension and diabetes, have been associated with cognitive decline in the absence of stroke or TIA.[1-4] Furthermore, cerebral pathologies with a presumed vascular etiology, such as MRI-defined infarcts and leukoaraiosis, are common in adults and are associated with lower cognitive function.[5-7] Whereas subclinical signs of vascular disease in other organ systems such as the heart are used routinely in the assessment of cardiovascular risk, it is uncertain whether tests of cognitive function could be similarly applied.

There are several measures of cognitive function that can be administered quickly, reliably, and with minimal expense, making them attractive candidates for tests that might further refine the clinical assessment of cardiovascular risk. Interpretation of cognitive test performance, however, is complicated by the influence of demographic factors such as age and education. We hypothesized that cognitive function below demographically adjusted norms may be an early manifestation of vascular end-organ injury and therefore identify individuals at risk for clinical cardiovascular events such as myocardial infarction (MI) and stroke. We tested this hypothesis in a middle-aged cohort from the Atherosclerosis Risk in Communities (ARIC) Study that was without known cardiovascular disease at the time of cognitive testing.

Methods. The ARIC Study is a population-based, prospective cohort study of cardiovascular disease in four US communities: Forsyth County, NC, Jackson, MS (African Americans only), suburban Minneapolis, MN, and Washington County, MD. Complete details of study methods and recruitment have been published previously.[8] In brief, 15,792 men and women ages 45 to 64 were recruited from 1987 to 1989. A comprehensive baseline clinic examination (Visit 1) was performed at enrollment, and follow-up contact consisted of annual telephone interviews and in-person clinic visits at 3-year intervals. All participants provided written informed consent, and the institutional review boards of each field center approved all study protocols. This analysis used the ARIC limited-access dataset in which variables that might allow individual participants to be identified are removed or modified and was approved by the Human Subjects Review Board of the University of California, San Francisco.

A baseline cognitive assessment was performed at the first follow-up visit (Visit 2) in 14,069 participants. The cognitive assessment consisted of three standardized neurocognitive tests: the

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Digit-Symbol Substitution Subtest of the Wechsler Adult Intelligence Scale–Revised (DSST),[9] the Delayed Word Recall (DWR) Test,[10] and the Word Fluency (WF) Test.[11] The DSST is a timed, written test that requires the participant to translate numbers into symbols using a key. The test score is based on the number of correct translations performed in a 90-second interval. The DWR score is based on recall of 10 common nouns after a 5-minute interval. The WF score is the number of words generated in three separate 1-minute trials beginning with the letters F, A, and S. Testing was performed by trained personnel, and interviews were recorded by study coordinators for quality control.

Vascular risk factor assessment and incident cardiovascular events. Blood pressure was measured three times after a 5-minute rest using a mercury sphygmomanometer, and the average of the second two measurements was used for the analysis. Hypertension was defined as a systolic blood pressure of >140 mm Hg, a diastolic blood pressure of >90 mm Hg, or self-reported use of antihypertensive medications. A 12-lead EKG was performed at rest, and the voltage and duration of the waveforms were determined by computer analysis at the ARIC Electrocardiogram Reading Center.[12] Left ventricular hypertrophy (LVH) on EKG was defined according to Sokolow–Lyon criteria.[13] Participants were asked to fast for 12 hours prior to each visit, and a venous blood sample was obtained and analyzed for plasma lipids and glucose at a central laboratory.[14] Diabetes was defined as a fasting blood glucose level of ≥126 mg/dL, a nonfasting glucose level of ≥200 mg/dL, or a self-reported history of diabetes or hypoglycemic medication use. Tobacco use was evaluated by questionnaire. In addition to the characterization of individual vascular risk factors, we used an established scoring system to calculate the Framingham risk score for each participant.[15] This risk score is based on a gender-specific weighting of the following vascular risk factors: age, systolic blood pressure, diastolic blood pressure, diabetes, tobacco use, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol. Vascular risk factor information was abstracted in >98% of participants at the time of cognitive testing (Visit 2) or, when missing, from the baseline visit (Visit 1).

We used a combination of medical history information, clinical findings, and study records to identify those without prevalent cardiovascular disease at the time of cognitive testing. Participants were excluded from the analysis if there was a self-reported history of MI, stroke, TIA, arterial surgery, angioplasty, or adjudicated MI on EKG at Visit 1 or an adjudicated MI, cardiac procedure, stroke, TIA, or new MI on EKG occurring between Visit 1 and Visit 2.

Detailed descriptions of the case ascertainment and cohort surveillance methods used in ARIC have been previously described.[16] In brief, cases were identified through annual contact of participants, searching discharge lists from local hospitals, and by reviewing death certificates. For hospitalizations with International Classification of Disease codes that indicated a possible MI, trained abstractors recorded relevant information including presenting signs and symptoms and cardiac enzymes. Side-by-side comparison of serial 12-lead EKGs was performed when possible. In potential cases of stroke, both a physician reviewer and an automated diagnostic system analyzed information from medical records, laboratory results, cerebrovascular imaging studies, and autopsy reports. When there was a discrepancy in diagnosis between the physician reviewer and the automated system, a second physician reviewer adjudicated the event.[17] Follow-up information was available through calendar year 1997. All potential CHD and stroke events were classified as definite, probable, or suspect according to standardized criteria.[16,18]

Incident cardiovascular events were defined as a definite or probable stroke, MI, or definite CHD death that occurred after cognitive testing.

Demographic adjustment of cognitive test scores. The primary predictor in our analyses was an adjusted cognitive test score defined as the ratio of observed (O) cognitive test scores to expected (E) cognitive test scores. Expected cognitive test scores were calculated using a participant's age, race (nonwhite vs white), gender, and education (at least some college, high school, or vocational school vs incomplete high school) after first estimating associations between these demographic factors and cognitive test performance within the study cohort using multivariable linear regression. O/E ratios of cognitive test scores were calculated separately and were approximately normally distributed for each of the three cognitive tests. We used the O/E ratio to represent an individual's cognitive test performance relative to a demographically similar peer group: Individuals with an O/E ratio of >1 are those who are performing above the average of their peers, and those with an O/E ratio of <1 are those whose performance is below the average of their peers.[19] This ratio is similar to the information that could be obtained by comparing cognitive test results with published norms based on demographic factors such as age and education. For example, younger, more educated individuals could be identified as low performers using this ratio even when their raw scores would place them near the average for the entire cohort. We then evaluated whether this ratio, as opposed to an individual's absolute performance on cognitive tests, was a predictor of subsequent cardiovascular risk.

Statistical methods. Continuous variables were compared with the independent samples t test, and categorical variables were compared with the Pearson χ^2 test. Cross-sectional associations between adjusted cognitive scores and Framingham risk scores were assessed using the Pearson product–moment correlation coefficient. The risk of incident cardiovascular events associated with quartile of adjusted cognitive test scores was studied using Cox proportional hazards analysis to estimate hazard ratios (HRs) with 95% CIs. Linear trend by quartile was assessed using a likelihood ratio test. The time to an event was defined as the time from completion of cognitive testing to the occurrence of an adjudicated MI, stroke, or CHD death. Participants were censored from the analysis at death, study dropout, or at the time of final contact. All multivariable models included terms for the following covariates unless otherwise noted: age, race (nonwhite vs white), gender, and education (at least some college, high school, or vocational school vs incomplete high school). We decided a priori to include demographic factors in the multivariable models to reduce the risk of residual confounding and to provide an estimate of the association of O/E ratios with cardiovascular disease that was independent of demographic characteristics. Covariates for the following vascular risk factors were entered and remained in models as a single group: hypertension, diabetes, current smoking status, LDL and HDL cholesterol, and LVH on EKG. The proportional hazards assumption was examined using both graphical and analytical methods and was adequately met.[20] We also performed a planned stratified analysis in which the association between quartile of adjusted cognitive scores and incident cardiovascular events was analyzed separately by quartile of baseline Framingham risk score. The significance of the interaction between Framingham and adjusted cognitive test score quartiles was determined using Cox proportional hazards analysis. All reported p values are two sided. All analyses were performed using the STATA statistical package (version 7.0; Stata Corp., College Station, TX).

Results. Of the 14,069 participants who completed cognitive testing, 12,185 had no history of prevalent cardiovascular disease. An additional 93 participants were excluded owing to missing demographic or medical history data, and therefore 12,096 participants were included in the analysis. Baseline demographic, cognitive, and vascular risk factor information for included participants are presented in table 1. As expected, included participants were younger, had higher levels of cognitive function, and had a lower burden of vascular risk factors at baseline when compared with ARIC cohort participants who did not meet inclusion criteria ($p < 0.01$ for all comparisons).

Within each quartile of adjusted cognitive test performance, there was a wide range of raw cognitive test scores, reflecting strong associations between demographic factors and cognitive test scores within the cohort. For example, within the lowest quartile of adjusted DSST performance, the median raw DSST score was 41 correct symbols among those ages 48 to 52 who had a college education as compared with 25 correct symbols among participants ages 62 to 67 who had not completed high school. Similar differences were seen between these groups in both the WF Test

Table 1 *Baseline cohort characteristics*

Characteristic	Included, n = 12,096	Excluded, n = 3,696*
Age†	57 (5.7)	58 (5.7)
Female	57	49
Nonwhite	25	35
College education, y	38	28
Systolic blood pressure, mm Hg	121 (19)	125 (22)
Diastolic blood pressure, mm Hg	72 (10)	73 (13)
Diabetes, n	14	23
Current tobacco use, n	22	32
EKG LVH‡	5	9
LDL cholesterol, mg/dL	133 (37)	136 (40)
HDL cholesterol, mg/dL	50 (17)	48 (17)
Digit-Symbol Substitution (correct symbols)	45 (14)	41 (14)
Delayed Word Recall (words recalled)	7 (1.5)	6 (1.5)
Word Fluency (names generated in 3 trials)	33 (13)	32 (12)

Values are means (SD) or percentages.

* Excluded participants were those who did not complete cognitive testing (n = 1,719), had a history of cardiovascular disease at the time of cognitive testing (n = 1,884), or had missing data (n = 93). All between-group differences were significant at $p < 0.01$.
† Age at time of cognitive testing, if completed.
‡ Left ventricular hypertrophy (LVH) on EKG by Sokolow–Lyon criteria.

LDL = low-density lipoprotein; HDL = high-density lipoprotein.

(median words listed: 26 vs 17) and the DWR (median words recalled: 6 vs 4).

During 75,291 person-years of follow-up (median follow-up 6.4 years), there were 516 incident cardiovascular events (292 fatal and nonfatal MIs, 50 CHD deaths, and 174 strokes) for an average annual incidence rate of 0.7%. Individuals with incident cardiovascular events had higher baseline Framingham risk scores when compared with other included participants (8.9 vs 6.4 points; $p < 0.001$). Baseline Framingham risk scores were not different when individuals with incident cardiac events were compared with those with incident stroke (8.8 vs 9.0 points; $p = 0.54$). There were 387 noncardiovascular deaths and 22 individuals were lost to follow-up, resulting in a total of 409 censored observations (3.4% of total). Individuals who were censored were older, had higher baseline Framingham risk scores, and had lower adjusted cognitive test scores than other included participants ($p < 0.001$ for each comparison).

When the adjusted DSST scores were modeled by quartile, the HR for cardiovascular events for those in the lowest quartile compared with the highest was 1.78 (95% CI 1.41 to 2.26, $p < 0.001$). Results were similar for comparisons between lowest and highest quartile scores for both the adjusted DWR (HR 1.46, 95% CI 1.15 to 1.85, $p < 0.001$) and the adjusted WF (HR 1.47, 95% CI 1.15 to 1.87, $p < 0.001$). After controlling for established vascular risk factors, the relationships between adjusted cognitive test scores and incident cardiovascular events were only mildly attenuated (lowest vs highest quartile adjusted DSST score, HR 1.56, 95% CI 1.23 to 1.97, $p < 0.001$) (table 2). Results were similar if demographic factors were left out of the multivariable models (data not shown). For comparison, the relative hazard for cardiovascular events for those with LVH on EKG was 1.49 (95% CI 1.23 to 1.97) in the same multivariable model (table 3). Similar relationships

Table 2 *Risk of cardiovascular events associated with baseline cognitive test scores**

		Hazard ratio for cardiovascular events (95% CI)			
Cognitive test	Quartile	Model 1†	*p* value‡	Model 2§	*p* value‡
Digit-Symbol Substitution	4	1.00 (ref.)		1.00 (ref.)	
	3	1.07 (0.81–1.41)	<0.001	1.02 (0.78–1.35)	<0.001
	2	1.29 (1.00–1.68)		1.23 (0.94–1.60)	
	1	1.78 (1.41–2.26)		1.56 (1.23–1.97)	
Word Fluency	4	1.00 (ref.)		1.00 (ref.)	
	3	1.00 (0.76–1.31)	<0.001	0.89 (0.68–1.17)	0.004
	2	1.49 (1.17–1.91)		1.31 (1.03–1.69)	
	1	1.47 (1.15–1.87)		1.28 (1.01–1.64)	
Delayed Word Recall	4	1.00 (ref.)		1.00 (ref.)	
	3	1.05 (0.81–1.37)	<0.001	1.00 (0.76–1.30)	0.004
	2	1.21 (0.94–1.57)		1.17 (0.90–1.51)	
	1	1.46 (1.15–1.85)		1.37 (1.08–1.74)	

* For each cognitive test, hazard ratios were calculated using the highest quartile of adjusted cognitive test scores as the reference.
† Model 1 includes covariates for age, race, gender, and education.
‡ *p* value for linear trend by quartile.
§ Model 2 includes the covariates from Model 1 and for hypertension, diabetes, current tobacco use, low-density and high-density lipoprotein cholesterol, and left ventricular hypertrophy on baseline EKG.

Table 3 *Risk of cardiovascular events associated with adjusted DSST scores and established vascular risk factors**

Variable	Hazard ratio (95% CI)
DSST quartile 4	1.00 (ref.)
DSST quartile 3	1.02 (0.78–1.35)
DSST quartile 2	1.23 (0.94–1.60)
DSST quartile 1	1.56 (1.23–1.97)
Hypertension	2.04 (1.69–2.45)
Diabetes	2.06 (1.69–2.51)
Current tobacco use	2.01 (1.68–2.43)
LDL cholesterol >160 mg/dL	1.74 (1.45–2.09)
HDL cholesterol <35 mg/dL	1.53 (1.25–1.88)
EKG LVH†	1.49 (1.10–2.01)

* Hazard ratios for DSST quartiles were calculated using the highest quartile of adjusted DSST scores as the reference. The model also included variables for age, gender, race, and education.

† Left ventricular hypertrophy (LVH) on EKG by Sokolow–Lyon criteria.

DSST = Digit-Symbol Substitution Test; LDL = low-density lipoprotein; HDL = high-density lipoprotein.

between adjusted cognitive test scores and risk of cardiovascular events were seen when cardiac events and strokes were considered separately (lowest vs highest quartile adjusted DSST score, stroke HR 1.75, 95% CI 1.17 to 2.62, $p = 0.007$; incident MI or CHD death, HR 1.45, 95% CI 1.08 to 1.95, $p = 0.01$).

When the cohort was stratified by Framingham risk quartile at baseline, adjusted DSST score predicted incident cardiovascular events in those in the highest Framingham risk quartile but not in those in the lowest Framingham risk (p for interaction = 0.035) (figure). A similar trend in which adjusted cognitive test scores were associated with cardiovascular events primarily in those with higher degrees of baseline risk was also apparent for the WF Test (p for interaction = 0.165) but not for the DWR Test (p for interaction = 0.38). When vascular and demographic factors were considered individually, the risk of cardiovascular events associated with adjusted DSST score was higher in those with hypertension (p for interaction = 0.008) and in those who were older at baseline (p for interaction = 0.15).

Discussion. In a cohort of middle-aged adults who had no history of prior cardiovascular disease or stroke, we found that cognitive test scores predicted incident cardiovascular events independently of established vascular risk factors. Subjects in the lowest quartile of cognitive performance had a risk of cardiovascular events that was approximately 50% greater than the risk of those in the highest quartile of cognitive performance after adjustment for confounders. The magnitude of the association was comparable with other major risk factors for cardiovascular disease, such as LVH on EKG and an HDL cholesterol level of <35 mg/dL. Cognitive function appeared to be an indicator of susceptibility to established vascular risk factors as individuals with the highest levels of adjusted cognitive function had a low risk of cardiovascular disease regardless of their Framingham score.

Several findings in this analysis support our hypothesis that the association between cognitive function and cardiovascular disease is mediated by the relationship of cognitive function to subclinical cerebrovascular injury. First, we found that cognitive function had little predictive value for cardiovascular disease in those in the lowest Framingham risk quartile. Such individuals would be expected to have the lowest probability of having subclinical cerebrovascular injury, and therefore variations in cognitive function would be unlikely to reflect vascular injury or inform cardiovascular prognosis. In contrast, the risk associated with low cognitive performance was greatest in those with high Framingham scores at baseline where subclinical cerebrovascular injury is likely to be most prevalent. Second, the observation that adjusted DSST scores generally showed stron-

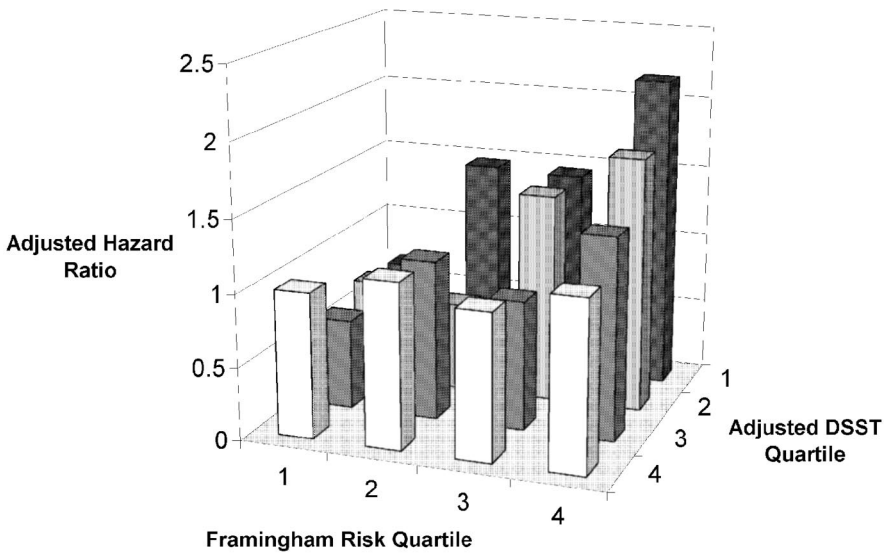

*Figure. Risk of cardiovascular events associated with adjusted Digit-Symbol Substitution Test (DSST) scores by Framingham risk quartile. All hazard ratios are adjusted for age, race, gender, education, hypertension, diabetes, tobacco use, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and left ventricular hypertrophy on baseline EKG. All hazard ratios are referenced to those in the highest adjusted DSST quartile and lowest Framingham risk quartile. The risk of cardiovascular events associated with adjusted DSST scores is greater in those with higher Framingham risk scores at baseline (*p *for interaction = 0.034).*

ger associations with cardiovascular risk than tests such as the DWR is consistent with prior studies that have demonstrated that measures of psychomotor speed like DSST are more sensitive indicators of cerebrovascular pathology than tests of verbal memory like DWR.[21] It is important to note, however, that there are other potential explanations for the observed association between cognitive test scores and cardiovascular prognosis. For example, individuals with low measures of cognitive function may be the most likely to be noncompliant with medications and therefore experience high cardiovascular event rates.[22]

Our results are consistent with several prior studies that have considered the relationship between cognitive function and stroke incidence. In both the Kungsholmen Project and the Established Populations for the Epidemiologic Studies of the Elderly, the risk of stroke increased with the severity of cognitive impairment.[23,24] Our cohort was younger than those of previous analyses, and therefore the association between cognitive test results and stroke is less susceptible to confounding from age-related comorbidities such as congestive heart failure.[25] A prior analysis of the ARIC cohort, however, reported that baseline cognitive function did not independently predict stroke incidence.[26] The prior analysis excluded >2,000 participants who were taking psychoactive medications and adjusted associations for multiple potential confounders not considered in this analysis, including carotid intimal–medial thickness and von Willebrand factor. As we hypothesized that lower than expected cognitive function was a potential marker of vascular injury (as opposed to a directly causative factor), statistical adjustment for other candidate cardiovascular risk factors was not performed. Additionally, our analysis had greater power to detect an association between cognitive function and the primary outcome as combined cardiovascular events were approximately three times as common as stroke in our study cohort.

The strengths of this study include its analysis of a large, community-based cohort that is well characterized with regard to vascular risk factors and cardiovascular outcomes. There are also several weaknesses. Although demographic norms by age, education, and gender are available for some cognitive tests, population norms are unlikely to be as accurate in identifying low performance in a given demographic as the study-specific demographic adjustment that was used in this analysis. However, when raw cognitive test scores were used in place of the adjusted cognitive test scores in the fully adjusted multivariable models, results were not materially different. Finally, residual or unmeasured demographic confounders may have influenced results.

The magnitude of the association between cognitive function and cardiovascular risk suggests that there is potential for cognitive testing to be useful in cardiovascular risk stratification. Although there are several new serum, genetic, and imaging-based markers of vascular risk that may ultimately prove more informative than cognitive testing for cardiovascular risk assessment, the cognitive tests used in ARIC may have advantages compared with these other tests based on their ease of administration and their lack of dependence on more expensive laboratory services. Whereas comparing cross-sectional results on cognitive function tests to demographic norms has inherent limitations as a way to identify acquired cognitive injury,[27] single measurements of cognitive function are more easily incorporated into the care of patients at risk for cardiovascular disease. Further studies are needed to determine whether a longitudinal determination of cognitive decline would be a more effective way to assess cardiovascular prognosis.

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Leukoencephalopathy from "chasing the dragon"

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A 49-year-old man developed confusion over approximately 1 week. He had regularly inhaled heroin heated over aluminum foil, a practice called "chasing the dragon." A neurologic examination revealed abulia, bradyphrenia, executive and short-term memory dysfunction, truncal ataxia, hyperreflexia, Babinski signs, and grasp reflexes. Brain MRI revealed confluent hyperintensities in the periventricular and subcortical white matter and the pons (figure). Blood test results were unremarkable. CSF had elevated myelin basic protein but no oligoclonal bands. Heroin-associated spongiform leukoencephalopathy (HASL) was diagnosed.

HASL is associated with repeated exposure to inhaled heated heroin vapor.[1] Pathologic studies reveal white matter spongiform degeneration with intramyelinic vacuolization.[1] On cranial MRI, HASL displays symmetric white matter hyperintensities involving the cerebrum, cerebellum, and brainstem on T2-weighted and fluid-attenuated inversion recovery images.[1,2]

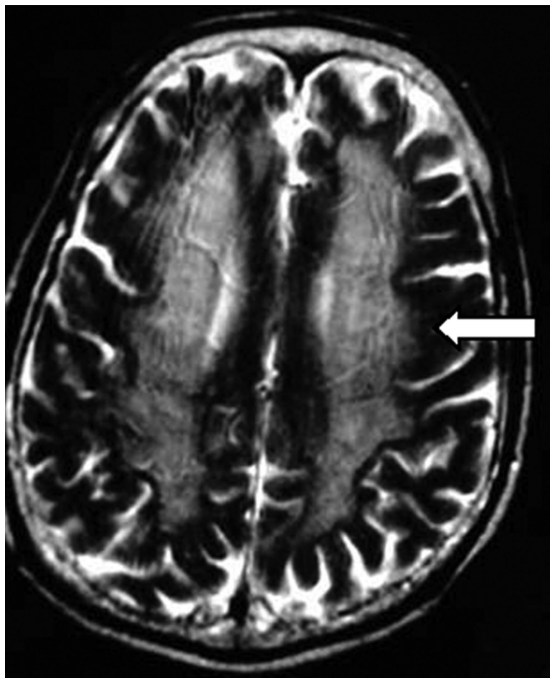

Figure. Axial T2-weighted image through the cerebral hemispheres shows confluent high signal hyperintensity in the subcortical white matter (arrow).

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