ORIGINAL CONTRIBUTION

The Age at Onset of Alzheimer's Disease and an Intracranial Area Measurement

A Relationship

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Objective: To examine the possibility that premorbid brain size may influence the age at onset of symptoms of Alzheimer's disease (AD).

Design: Retrospective case series.

Setting: Outpatients attending a memory disorders clinic in a tertiary referral center.

Patients: Twenty-eight female patients with the diagnosis of probable AD, selected for the availability of informant derived estimates of age at onset of symptoms and computed tomographic scans of the head satisfying angulation criteria.

Main Outcome Measure: An average intracranial area of two adjacent computed tomographic scan sections appropriately angled was used as a correlate of premorbid brain size. Strict intracranial volume measurement was not performed.

Results: Age at onset of symptoms of AD correlated positively (r=.48, P=.009) with our measure of premorbid brain size. There was no confounding by education, height, or ethnicity.

Conclusion: Premorbid brain size may be an important determinant of the age at onset of symptoms of AD. Epidemiologic studies of AD may need to assess the relationship between brain size and putative risk factors, eg, low educational attainment, since there is evidence that brain size is not distributed uniformly across populations.

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KATZMAN ET AL[1] identified a group of elderly women with the pathologic changes of Alzheimer's disease (AD) who were cognitively intact prior to death. The brains of these women were larger than the brains of cognitively impaired women with similar pathologic changes. Katzman et al speculated that the larger brains of the cognitively intact subjects may have provided a reserve against the consequences of the pathologic changes. We thought that there might be a more general relationship between brain size and the onset of cognitive changes in patients with AD, ie, that all individuals with AD may have functional reserve in direct proportion to their premorbid brain size.

The calvarium is a reactive organ; its size is determined solely by the volume of brain and meninx contained within it.[2] If the brain atrophies, the volume delimited by the inner table of the skull, nevertheless, stays constant.[3] The intracranial volume is, thus, an indicator of maximal mature brain size, even after the onset of aging and neurodegenerative processes. If premorbid brain size is a determinant of reserve, there should be a positive correlation between intracranial size and the age at onset of symptoms within a population of individuals with AD. Our study tests that prediction.

RESULTS

Patient characteristics are outlined in the **Table**. At the commencement of the study in March 1992, the registry of the Center for Alzheimer's Disease Research comprised 435 patients who had been examined since 1980; of these, 133 had probable AD by the strict National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Associa-

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PATIENTS AND METHODS

PATIENT SELECTION

Subjects in this study were selected by the following criteria.

Diagnosis of Probable AD

Patients were identified through the records of the Center for Alzheimer's Disease Research in New York City at Columbia–Presbyterian Medical Center. All patients were seen at the same memory disorders clinic. Brain magnetic resonance imaging or computed tomographic (CT) scans were obtained when there was significant cognitive impairment, unless scanning had recently been undertaken elsewhere. Based on the results of all clinical and laboratory tests, including comprehensive neuropsychologic evaluation, diagnosis was assigned at a consensus meeting of neuropsychologists and neurologists, according to the criteria established by the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association.[4] A modified Clinical Dementia Rating is used to indicate severity of the disease.[5]

Female Gender

The study was restricted to women, because a preliminary review of the Center for Alzheimer's Disease Research and Columbia–Presbyterian Medical Center Radiology Department records indicated that too few men would meet our selection criteria for a separate analysis by gender. We considered that analysis of combined data from both sexes would be inappropriate, because men have larger brains than do women on average,[6] and because there may have been other gender-associated factors besides brain size influencing the age at onset of symptoms.

Onset of Symptoms After the Age of 60 Years

Physicians documented the date of onset of symptoms at the patients' initial evaluation. This date was used to calculate the age at first symptom.

Availability of a Suitable CT Scan of the Head

A scan was deemed suitable if it consisted of transaxial sections paralleling the orbitomeatal line. This standard angulation was confirmed if the image containing the foramen of Monro was one section below the image containing the pineal gland. To be acceptable, a given CT scan also had to include an internal scale for measurement.

INTRACRANIAL MEASUREMENT

A standardized cross-sectional intracranial area was taken as a correlate of premorbid brain size. The areas from two adjacent CT sections were averaged, ie, the intracranial area at the level of the foramen of Monro and the intracranial area at the level of the pineal gland.

Two methods were used to quantify cross-sectional intracranial area. With the first method, the computer was instructed to count all pixels in a given image, with the CT number under 200 Hounsfield units (HU). Since the calvarium has a CT number greater than 200 HU, the inner soft tissues of the head were counted selectively. This technique for edge detection of the inner table of the skull provided the gold standard for estimation of intracranial area, but it required that raw data from the original scan be accessible. In the second method, the images were projected from the radiographic film onto graph paper (10×10 squares per inch grid), using an overhead projector. The inner table of the skull was then traced by hand, and the image scale was marked. We counted the squares within the tracing manually, calculated the proportional worth of a square from the scale, and arrived at a measure of actual intracranial area.

The computer-assisted area measurements were taken on all 18 study subjects for whom the raw data from the original scan were available. The corresponding overhead projected measurements correlated very highly (r=.93, P<.00001).

The overhead projected measurements were used in the subsequent analysis because they were available for all subjects. We will refer to the average area of the two chosen sections obtained in this way as *brain size*.

DATA ANALYSIS

Data were analyzed by computer (SPSS/PC+ 4.0 Base Manual for the IBM PC/XT/AT and PS/2, Norusis MJ/SPSS Inc, Chicago, Ill). The relationship between brain size and age at first symptom was evaluated using multiple linear regression,[7] with brain size as the independent variable, age at first symptom as the dependent variable, and education, height, and ethnic group as potential confounding variables that might be related to both brain size and age at onset.

tion criteria, 74 of whom were women. We excluded 22 subjects with onset of symptoms before age 60 years and three patients for whom onset of symptoms could not be estimated accurately because there was no informant. Of the remaining 49 patients, an additional 21 were excluded because they had magnetic resonance imaging scans only (n=2) or CT scans that were unavailable (n=9), lacked an internal scale (n=7), or were not properly angulated (n=3). The remaining 28 patients satisfied all our study criteria. One of the 28 patients was first seen in 1985. The remainder were first seen from 1988 to 1992. Twelve different physicians evaluated the patients at presentation to the clinic. Twenty-seven of the CT scans were performed on General Electric scanners and one on a Picker scanner. Computed tomographic sections were 5 mm thick with 2-mm intersection gaps in all cases except two; one scan consisted of 5-mm-thick sections with 5-mm intersection gaps, and the other was obtained using contiguous 7-mm-thick sections.

Brain size correlated positively with age at first symptom (r=.48, P=.009). Linear regression analyses with brain

Patient Characteristics

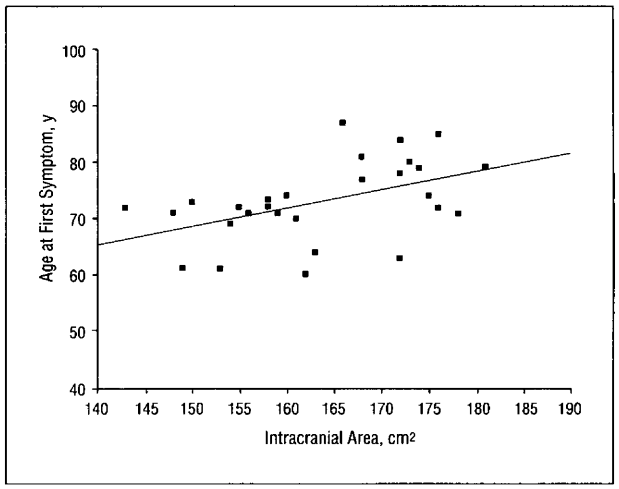
Characteristics	White	Black	All
n (%)	21 (75)	7 (25)	28 (100)
Height, cm			
Mean	157	166	159
SD	8	14	10
Range	142-175	142-183	142-183
Brain size, cm^2			
Mean	165.7	157.2	163.5
SD	10.3	8.7	10.3
Range	143-181	148-174	143-181
Education, y			
Mean	11.0	11.7	11.1
SD	3.6	4.3	3.8
Range	6-20	6-20	6-20
Age at onset, y			
Mean	73.7	71.0	73.0
SD	7.6	5.5	7.1
Range	60.1-87.1	60.8-79.1	60.1-87.1
Age at assessment, y			
Mean	76.9	73.8	76.1
SD	8.2	4.8	7.5
Range	62.9-89.8	66.4-82.7	62.9-89.8
Duration of symptoms, y			
Mean	3.2	2.8	3.1
SD	2.2	1.9	2.1
Range	0.5-9.6	1.0-5.7	0.5-9.6
Clinical dementia rating (CDR) Scale			
CDR 1	18	4	22
CDR 2	3	1	4
CDR 3	...	2	2

size as the only independent variable revealed that the onset of symptoms was delayed by a third of a year for each 1-cm^2 increase in brain size (95% confidence interval, 0.10-0.57). This relationship did not change when education, height, and ethnic group were included in the model (r=.64, P=.011). This model also predicted a 0.33-year delay (95% confidence interval, 0.10-0.56) in onset of memory problems for each 1-cm^2 increase in brain size. There was no association between brain size and educational attainment (r=−.06, NS). The **Figure** shows the graphic relationship between age at first symptom and brain size for all 28 subjects.

COMMENT

We found a significant, positive correlation between the age at onset of symptoms of AD and our standardized intracranial area measurement in 28 women presenting to a memory disorders clinic. Our finding lends support to the hypothesis that premorbid brain volume helps determine the reserve beyond which cognitive changes emerge in individuals with AD.

Our study has a number of limitations. The sample size is small, primarily because CT scans were not available for more patients. The estimates of age at first symptom and brain size are both subject to errors in measurement. Error in estimations of age at first symptom might arise for many reasons, including variation in informants' abilities to detect changes and variation in physicians' assessments of symptom onset, since no standardized historical probes were used to establish symptom onset, and 12 different physicians saw the 28 patients. We calculated only an imperfect estimate of premorbid brain size using the average area of two standardized CT scan sections. Volumetric measurements were not performed because of the retrospective nature of the study and technical difficulties associated with obtaining such measures from the available scans. Since AD is predominantly a forebrain cortical process, it would have been interesting to measure not just total intracranial volume but supratentorial intracranial volume in particular, to provide a volumetric estimate of premorbid forebrain size. But such measurements cannot be obtained accurately from routine axial CT scans. Because of individual variation in the shape of the calvarium, there might have been differences in intracranial volumes between subjects, differences that were not adequately reflected by an area measurement. Similarly, ethnic differences in skull shape could have led to systematic error when an area measure was used to assess volume, although the effect of an ethnic group was not significant when it was included as an independent variable in the analysis.



Relationship between the standardized cross-sectional intracranial area (brain size) and the age at first symptom of Alzheimer's disease.

We are unaware of any published epidemiologic studies of the incidence or prevalence of AD that have assessed intracranial volume or its correlates as significant antecedent factors. The results of our limited, clinic-based investigation suggest that premorbid brain volume might be an important variable to consider; if it is a determinant of AD symptom onset, then the age-specific incidence of AD might differ between strata defined by premorbid brain volume. In our small, select study population, there was no association between brain size and educational attainment, although one might have been anticipated from the results of other investigations. In two recent magnetic resonance imaging studies,[8,9] mature brain volume was shown to correlate positively with IQ test performance, which itself correlates positively with educational attainment.[10] In another study,[10] socioeconomic status correlated with a standardized head CT scan section area, with upper social class individuals having, on average, larger section areas.[11] Since educational attainment is one measure of socioeco-

nomic status,[12] this finding also suggests that brain volume may correlate positively with educational attainment when large, representative populations are examined.

In conclusion, premorbid brain volume may be a determinant of cognitive reserve in patients with AD, and it may emerge as an important antecedent factor for AD in future epidemiologic studies. Such studies would also need to assess the relationship between premorbid brain volume and putative risk factors, such as low educational attainment,[13-16] to identify possible confounding or interaction.

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REFERENCES

1. Katzman R, Terry R, DeTeresa R, et al. Clinical, pathological, and neurochemical changes in dementia: a subgroup with preserved mental status and numerous neocortical plaques. *Ann Neurol.* 1988;23:138-144.
2. Moss ML. Functional cranial analysis and the functional matrix. *Int J Orthod.* 1979;17:21-31.
3. Davis PJM, Wright EA. A new method for measuring cranial cavity volume and its application to the assessment of cerebral atrophy at autopsy. *Neuropathol Appl Neurobiol.* 1977;3:341-358.
4. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report on the NINCDS-ADRDA work group under the auspices of the Dept of Health and Human Services Task Force on Alzheimer's Disease. *Neurology.* 1984;34:939-944.
5. Burke WJ, Miller JP, Rubin EH, et al. The reliability of the Washington University Clinical Dementia Rating. *Arch Neurol.* 1988;45:31-32.
6. Ho K-C, Roessmann U, Straumfjord JV, Monroe G. Analysis of brain weight, I: adult brain weight in relation to sex, race, and age. *Arch Pathol Lab Med.* 1980; 104:635-639.
7. Neter J, Wasserman W, Kutner MH. *Applied Linear Regression Models.* 2nd ed. Homewood, Ill: Richard D Irwin Inc; 1989.
8. Willerman L, Schultz R, Rutledge JN, Bigler ED. In vivo brain size and intelligence. *Intelligence.* 1991;15:223-228.
9. Andreasen NC, Flaum M, Swayze V II, et al. Intelligence and brain structure in normal individuals. *Am J Psychiatry.* 1993;150:130-134.
10. Jencks C, Smith M, Acland H, et al. Path models of intergenerational mobility. In: Jencks C, ed. *Inequality: a Reassessment of the Effect of Family and Schooling in America.* New York, NY: Basic Books Inc; 1972:320-350.
11. Pearlson GD, Kim WS, Kubos KL, et al. Ventricle-brain ratio, computed tomographic density, and brain area in 50 schizophrenics. *Arch Gen Psychiatry.* 1989;46:690-697.
12. Liberatos P, Link BG, Kelsey JL. The measurement of social class in epidemiology. *Epidemiol Rev.* 1988;10:87-121.
13. Zhang M, Katzman R, Salmon D, et al. The prevalence of dementia and Alzheimer's disease in Shanghai, China: impact of age, gender, and education. *Ann Neurol.* 1990;27:428-437.
14. Snowden DA, Ostwald SK, Kane RL. Education, survival, and independence in elderly Catholic sisters, 1936-1988. *Am J Epidemiol.* 1989;130:999-1012.
15. Banaiuto S, Rocca WA, Lippi A, et al. Impact of education and occupation on prevalence of Alzheimer's disease (AD) and multi-infarct dementia (MID) in Appignano, Macerata Province, Italy. *Neurology.* 1990;40(suppl 1):346.
16. Fratiglioni L, Grut M, Forsell Y, et al. Prevalence of Alzheimer's disease and other dementias in an elderly urban population: relationship with age, sex, and education. *Neurology.* 1991;41:1886-1892.