ORIGINAL CONTRIBUTION

White Matter Lesions and Disequilibrium in Older People

I. Case-Control Comparison

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Objective: To investigate the relationship between subcortical white matter lesions identified on magnetic resonance imaging and gait and balance problems in older people.

Design: Magnetic resonance imaging scans of the brain in 27 community-dwelling older patients (>75 years of age) who had subjective and objective abnormalities of gait and balance of unknown cause were compared with those of 27 age- and sex-matched control subjects. The T_2-weighted intense lesions of the subcortical white matter were graded on a scale of 0 to 2.

Setting: Outpatient clinic.

Results: The patients had significantly ($P<.01$, χ^2) more severe subcortical white matter hyperintensities on magnetic resonance imaging than did the control group. Patients fell more frequently than did the control subjects and had slower motor responses and prolonged reaction times compared with the control subjects.

Conclusions: Subcortical white matter lesions identified on magnetic resonance imaging are associated with gait and balance dysfunction in ambulatory older people. These lesions probably interfere with central processing of sensorimotor signals leading to impaired postural responses.

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HIGH-INTENSITY signal lesions on T_2-weighted magnetic resonance imaging (MRI) of the cerebral white matter are common in older people.[1-6] These lesions increase in frequency and severity with age, but there is controversy regarding their pathophysiologic significance. Although some investigators have found a relationship between the white matter lesions and cognitive[6-11] or motor deficits,[12-15] others have not.[3,16,17] Use of the term *unidentified bright objects*[5] epitomizes the diagnostic uncertainties associated with these white matter lesions.

Balance and gait disorders are also common in older people, and it can be difficult to ascribe a specific cause for these problems even after a thorough clinical evaluation.[18] The extensive subcortical white matter disease associated with severe hypertension (subcortical arteriosclerotic encephalopathy [Binswanger's disease]) causes a characteristic abnormality of gait with elements of both parkinsonism and ataxia.[12] If extensive white matter lesions cause a profound gait abnormality, earlier stages of white matter lesions may cause a milder, more subtle gait abnormality. To address this question, we identified a group of fully functional older people with mild but documented gait and balance dysfunction and compared the degree of deep white matter lesions on MRI with those of an age-matched control group who had normal gait and balance.

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RESULTS

CLINICAL DATA

Hypertension by clinical history and by measurement at the time of the MRI occurred with about equal frequency in the disequilibrium group and control groups (**Table 1**). Falls, particularly multiple falls, were more common in the patient group than in the control group (Table 1). Most falls in both groups were attributed to accidental slips or trips. Eleven patients and two control subjects reported at least one

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PATIENTS AND METHODS

PATIENTS

As part of a prospective study on dizziness and disequilibrium in older people sponsored by the National Institute on Aging, Bethesda, Md, we are conducting a follow-up study of 100 patients older than 75 years who complain of dizziness and/or disequilibrium. This study was approved by the appropriate institutional review board, and all subjects signed an informed consent form. Details regarding the patient selection and testing are described elsewhere.[18] About half were referred to the UCLA Medical Center, Los Angeles, Calif, for evaluation of dizziness or disequilibrium, and the other half were enrolled in response to a newspaper advertisement asking for people older than 75 years to participate in a study of balance and dizziness. From these 100 patients, we identified a subgroup of 27 patients who had disequilibrium of unknown cause and a Tinetti gait and balance score[19] of 24 or less (maximum score, 28). The total scores ranged from 10 to 24, with a mean score of 20.7±3.4. The other 73 patients did not complain of disequilibrium (30 patients), had disequilibrium of known cause (31 patients), or had a total score on the Tinetti scale greater than 24. We included patients who initially presented with benign positional vertigo but continued to complain of disequilibrium after the benign positional vertigo was successfully treated with a positional maneuver or positional exercises.[20] We also included patients with a remote history of vertigo but without any evidence of an ongoing neuro-otologic disorder (ie, normal auditory and vestibular function testing results).

CONTROL SUBJECTS

The control subjects were selected from a group of 100 normal older people who are undergoing follow-up with serial examinations in the same study mentioned above. All considered their balance to be normal. They were initially recruited through newspaper advertisements, and they have undergone the same extensive clinical evaluation performed on the patients. For each patient, a control subject was selected of the same sex and closest in age to the patient. To be considered, the control subject had to have a total score on the Tinetti scale of 27 or 28. All patients and control subjects were functioning independently with maximum scores on two activity of daily living scales.[21,22] The frequency of use of alcohol and sedating medications was comparable among patients and control subjects. All were paid for participation in the study.

CLINICAL EVALUATIONS

A history and neurologic examination, tests of visual acuity and orthostatic vital signs, questionnaire responses (including questions about hypertension and diabetes mellitus), the Mini-Mental State Examination,[23] a Tinetti gait and balance score,[1] a Purdue pegboard motor assessment,[24] and saccade reaction time[25] were performed on the same day as the MRI scan. For the Purdue pegboard motor assessment, each subject was graded on the number of pegs inserted in the board during 30 seconds using the dominant hand, the nondominant hand, and both hands. Saccade reaction time was measured with electro-oculography as the subjects followed a small laser target moving in a square wave pattern at pseudorandom frequency, amplitude, and direction.[25] Each subject was interviewed and asked about the circumstances of falls that occurred in the prior 12 months.

MRI CRITERIA

Brain MRI scans were obtained with a 1.5-T scanner (Signa, General Electric, Milwaukee, Wis). Multiple slice spin echo sequences were performed with a repetition time of 3000 milliseconds and an echo time of 100 milliseconds, producing a T_2-weighted image. Magnetic resonance imaging was performed in the axial plane with a slice thickness of five mm in all subjects. The MRIs were initially screened by a neuroradiologist to rule out other possible causes of balance and gait dysfunction. None were found. The MRIs were then analyzed independently by two different assessors who were blinded to all clinical information. To rate the white matter lesions on MRI, we chose the scale described by Breteler et al[9] (attributed to Caplan and van Swieten) after our initial assessment found it to be reliable and reproducible. The criteria used were 0, no or slight periventricular hyperintensity (small caps or pencil-thin lining), fewer than five focal lesions and no confluent lesions; 1, moderate periventricular hyperintensity (caps on both anterior and posterior horns of the lateral ventricles, corpus only partially involved, not irregularly extending into the deep white matter) or five or more focal lesions, or both, but no confluent lesions; and 2, severe periventricular hyperintensity (irregularly extending into the deep white matter or marked areas of hyperintensity completely surrounding the lateral ventricles) or confluent lesions regardless of the presence of focal lesions. Agreement between the two assessors was complete with respect to absence (grade 0) or presence (grade 1 or 2) of white matter lesions, and good with respect to the distinction between grade 1 and 2 severity of lesions (there was initial disagreement in six instances, but consensus was reached after review and discussion while the assessors were still blinded to clinical data).

fall owing to loss of balance. None reported falls owing to dizzy spells or drop attacks. There was no significant difference in the mean Mini-Mental State status score in the two groups, with only two subjects in each group having a score less than 26. The slightly lower mean score in the disequilibrium group can be attributed to a single patient with a score of 13. Motor performance assessed with the Purdue pegboard was consistently better in the control subjects than in the disequilibrium group, but the difference between the two groups was only significant when comparing the performance of the nondominant hand (Table 1). Finally, measurements of saccade

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reaction time were significantly longer in the disequilibrium group compared with control subjects (Table 1).

Table 1. Comparison of Clinical Data in Patients and Control Subjects*

Feature	Patients (n=27)	Control Subjects (n=27)
Age, y	82.0±3.9	81.2±2.7
Female-male ratio	15:12	15:12
Hypertension, mm Hg		
By history	9	8
Diastolic, >90	7	4
Systolic, >160	8	7
Diabetes mellitus (noninsulin dependent)	3	0
Falls in prior year		
≥1 fall	20	11
>2 falls	10	0
Fell owing to loss of balance	11	2
Tinetti score		
Total (maximum, 28)	20.7±3.4	27.7±0.5
Balance (maximum, 16)	11.2±2.0	15.7±0.5
Gait (maximum, 12)	9.5±1.7	11.9±0.2
Mini-Mental State score (maximum, 30)	27.9±3.2	28.7±1.5
Purdue pegboard (No. of pegs)		
Dominant	10.0±1.8	10.8±1.7
Nondominant	9.0±1.3	10.5±1.6†
Both	13.6±3.0	15.6±3.2
Saccade reaction time, ms	228±50	199±28‡

*Number of subjects or mean±1 SD.
†P<.01, Bonferroni corrected post hoc Student's t test.
‡P<.05, Bonferroni corrected post hoc Student's t test.

Table 2. Prevalence of White Matter Lesions in the Patient and Control Groups

Grade	Patients, No.	Control Subjects, No.
0,* No/slight	3	12
1,† Moderate	10	12
2,‡ Severe	14	3

*Fewer than five focal lesions, no/slight periventricular hyperintensities, and no confluent lesions.
†Fewer than five focal lesions, moderate periventricular hyperintensities, and no confluent lesions; or at least five focal lesions and no/slight/moderate periventricular hyperintensities, but no confluent lesions.
‡Confluent lesions and/or severe periventricular hyperintensities.

MRI WHITE MATTER LESIONS

The patient group had significantly more severe white matter lesions than did the control subjects ($P<.01$, χ^2)(**Table 2**). Fourteen patients were rated as having severe white matter lesions (grade 2), while only three control subjects had severe lesions. Typical MRIs illustrating the three degrees of white matter lesions are shown in the **Figure**.

We divided the patient group into two subgroups of approximately equal size, one with severe white matter lesions (grade 2) and the other with less severe white matter lesions (grades 0 and 1) and compared the performance of the two subgroups (**Table 3**). Although, on average, those with severe white matter lesions performed more poorly than did those with less severe lesions on all tests, the difference was significant ($P<.05$) only for the Tinetti total gait and balance score and for the saccade reaction time measurements.

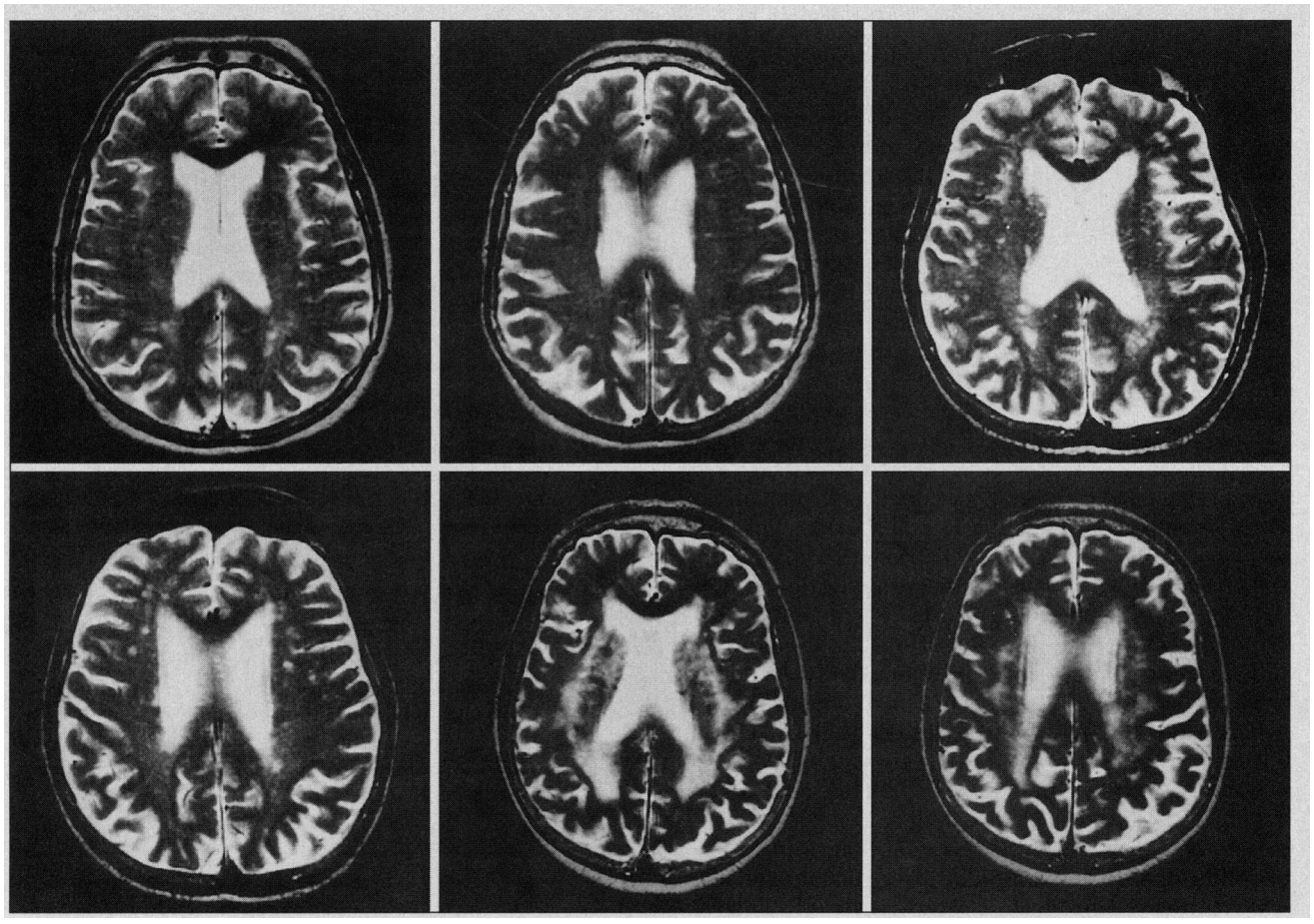
COMMENT

RISK FACTORS FOR WHITE MATTER LESIONS

Although hypertension has clearly been associated with subcortical white matter lesions in other studies,[1,8,9] we did not find a significant difference in the incidence of hypertension (by history or measured at the time of the MRI) in the patient and control groups. The age range of our study population probably explains this apparent conflict of findings. Breteler et al[9] studied a random sample of 111 subjects between the ages of 65 and 84 years and found that both systolic and diastolic blood pressure were significantly associated with white matter lesions in subjects 65 to 74 years of age but not in those 75 to 84 years of age. All of our subjects were older than 75 years and most were older than 80. The increased incidence of myocardial infarction, stroke, and other vascular disease associated with hypertension leads to a decreased survival of hypertensive patients into their 80s. Therefore, although hypertension is an important cause of subcortical white matter lesions, fewer patients with white matter lesions secondary to hypertension live into their 80s. Other pathophysiologic mechanisms must be important in the genesis of white matter lesions in this older population.[9] Diabetes mellitus is a risk factor for white matter lesions, but only three patients and no control subjects had a history of adult-onset diabetes mellitus. Of the three patients, two had a white matter lesion score of 2, and the other had a white matter lesion score of 1.

DO WHITE MATTER LESIONS CAUSE GAIT AND BALANCE ABNORMALITIES?

Most prior studies assessing the clinical significance of subcortical white matter lesions on MRI have focused on cognitive function, but a few studies have focused on the possible association with gait and balance abnormalities. Thompson and Marsden[12] described 12 patients (age range, 60 through 82 years) who presented with severe gait problems that Thompson and Marsden attributed to subcortical arteriosclerotic encephalopathy (Binswanger's disease). All patients had hypertension and symmetrical low attenuation of cerebral white matter throughout the frontal and parietal regions on computed tomography of the brain. Lacunar infarcts were identified in four patients. The gait abnormalities varied from those who could walk without support to those who could not even stand without support. They described a characteristic gait pattern with elements similar to that of patients with hydrocephalus, frontal lobe lesions, and so-called senile gait of the elderly. The difficulty in using their legs to walk was out of proportion to that of other movements of the lower limbs when lying or sitting and to the relatively preserved upper limb mobility and facial expression. They assumed that the deep white matter lesions



Magnetic resonance images illustrating three stages of white matter lesions. Top left and top center, grade 0, no/slight; top right and bottom left, grade 1, moderate; and bottom center and bottom right, grade 2, severe.

Table 3. Comparison of Clinical Data in Patients With Low-Grade (0 or 1) and High-Grade (2) White Matter Lesions on MRI

Feature	Grade 0 or 1 (n=13)	Grade 2 (n=14)
Age, y	81.5±4.2	82.8±3.3
Female-male ratio	8:5	7:7
Tinetti score total	21.8±2.3	19.7±4.0†
Mini-Mental State score	28.7±0.9	27.2±4.4
Purdue pegboard (No. of pegs/30 s)		
Dominant	10.2±1.7	9.8±1.9
Nondominant	9.4±1.4	8.7±1.8
Both	14.0±3.3	13.2±2.7
Saccade reaction time, ms	207±35	250±53†

**MRI indicates magnetic resonance imaging.*
†P<.05, Bonferroni corrected post hoc Student's t test (two-tailed).

interrupted afferent and efferent projections of the leg areas of motor cortex and supplementary motor area. The patients described by Thompson and Marsden[12] were clearly more severely affected than our patients and overall had more diffuse white matter disease.

Masdeu et al[14] compared quantitative scores of gait and balance with deep white matter lesions identified on computed tomography in 40 older subjects without evidence of the neurologic disease known to be associated with falls. Twenty subjects who were prone to falling were compared with 20 control subjects who were not prone to falling, all recruited from a nursing home. Those likely to fall were identified by reviewing incident reports in the nursing home. The mean age (±1 SD) of the those likely to fall was 84.3±1.5 years, and the mean age of the control subjects was 81.5±2.0 years. The group of those who had a tendency to fall had significantly worse gait and equilibrium scores and a greater degree of deep white matter lesions on computed tomography. Furthermore, the degree of white matter lesions correlated with the degree of impaired gait and equilibrium but not with the performance on cognitive testing. We studied noninstitutionalized subjects in the same age range using MRI and came to similar conclusions.

Hennerici et al[15] compared quantitative measures of gait and periventricular white matter lesions identified on MRI in a group of 24 patients meeting the clinical criteria for vascular dementia. All patients had abnormalities of gait, and the quantitative measurements were significantly correlated with frontal periventricular white matter lesions on MRI. The authors suggested that gait disturbances due to white matter lesions involving the thalamocorticomediocapsular pathways may precede the more diffuse involvement associated with dementia.

OTHER CAUSES OF PATIENTS' DISEQUILIBRIUM

The increased incidence of severe deep white matter hyperintensities on MRI suggests that the white matter lesions were important in the pathophysiology of the disequilibrium in at least some patients. However, three patients had no or slight deep white matter lesions, and 10 had only moderate lesions. Other factors must have contributed to these patients' disequilibrium. Although patients with bilateral vestibular loss, visual loss, or clinically apparent peripheral neuropathy were excluded from the study, it is possible that partial loss of vestibular, visual, and somatosensory function, each of which was not outside the normal limit, contributed to the disequilibrium (so-called multisensory dizziness).[18] Early midline cerebellar degeneration can also present as disequilibrium without other neurologic findings.[26] However, this condition typically results in a characteristic combination of eye movement abnormalities including gaze-evoked or downbeat nystagmus, symmetrically impaired smooth pursuit and optokinetic responses, and reduced ability to suppress the vestibulo-ocular reflex by fixation. None of the patients or control subjects had this combination of oculomotor abnormalities, and none had cerebellar atrophy on MRI.

PATHOPHYSIOLOGY OF THE DISEQUILIBRIUM

Central somatosensory conduction time increases with age and may result in less-efficient integration of sensory information and execution of postural responses.[27] Kluger et al[11] and Ylikoski et al[7] studied normal older subjects and found a significant negative correlation between the severity of subcortical white matter lesions and the performance on neuropsychological tests that focused on the speed of neural processing. The latter study[7] also found a significant negative correlation between the speed of finger tapping (with either hand) and the severity of white matter lesions. We measured saccade latency as an indicator of central reaction time and found a significant prolongation in patients compared with control subjects. Furthermore, within the patient group those with more severe white matter lesions (grade 2) had significantly longer saccade reaction times than did those with less severe lesions (grades 0 and 1).

The typical features of gait in our patients were a slight widening of the base, slowing and shortening of stride length, and turning en bloc. Nutt et al[28] called this gait disorder a "cautious gait" because they felt it represented a nonspecific reaction to disequilibrium and imbalance rather than an indicator of a localized central nervous system lesion. Whether the white matter lesions identified on MRI interfered with specific motor pathways as suggested by Thompson and Marsden[12] and by Masdeu et al[14] or whether they simply interfered with the long loop reflexes that transverse the periventricular white matter to produce nonspecific interruption of sensorimotor integration is unclear. Regardless of the mechanism, however, our data provide convincing evidence that subcortical white matter lesions in older people are associated with abnormalities of balance and gait and with an increased likelihood of falling.

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REFERENCES

1. Awad IA, Spetzler RF, Hodak JA, Awad CA, Carey R. Incidental subcortical lesions identified on magnetic resonance imaging in the elderly, I: correlation with age and cerebrovascular risk factors. *Stroke.* 1986;17:1084-1089.
2. Fazekas F. Magnetic resonance signal abnormalities in asymptomatic individuals: their incidence and functional correlates. *Eur Neurol.* 1989;29:164-168.
3. Hunt AL, Orrison WW, Yeo RA, et al. Clinical significance of MRI white matter lesions in the elderly. *Neurology.* 1989;39:1470-1474.
4. Mirsen TR, Lee DH, Wong CJ, et al. Clinical correlates of white matter changes on magnetic resonance imaging scans of the brain. *Arch Neurol.* 1991;48:1015-1021.
5. Kertesz A, Black SE, Tokar G, et al. Periventricular and subcortical hyperintensities on magnetic resonance imaging: 'rims, caps, and unidentified bright objects.' *Arch Neurol.* 1988;45:404-408.
6. Guerriero Austrom M, Thompson RF, Hendrie HC, et al. Foci of increased T_2 signal intensity in MR images of healthy elderly subjects: a follow-up study. *J Am Geriatr Soc.* 1990;38:1133-1138.
7. Ylikoski R, Ylikoski A, Erkinjuntti T, et al. White matter changes in healthy elderly persons correlate with attention and speed of mental processing. *Arch Neurol.* 1993;50:818-824.
8. van Swieten JC, Geykes GG, Derix MMA, et al. Hypertension in the elderly is associated with white matter lesions and cognitive decline. *Ann Neurol.* 1991;30:825-830.
9. Breteler MMB, van Swieten JC, Bots ML, et al. Cerebral white matter lesions, vascular risk factors, and cognitive function in a population-based study: the Rotterdam Study. *Neurology.* 1994;44:1246-1252.
10. Boone KB, Miller BL, Lesser IM, et al. Neuropsychological correlates of white-matter lesions in healthy elderly subjects: a threshold effect. *Arch Neurol.* 1992;49:549-554.
11. Kluger A, Gianutsos J, Leon MJ, George AE. Significance of age-related white matter lesions. *Stroke.* 1988;19:1054-1055.
12. Thompson PD, Marsden CD. Gait disorder of subcortical arteriosclerotic encephalopathy: Binswanger's disease. *Move Disord.* 1987;2:1-8.
13. Kinkel WR, Jacobs L, Polachini I, Bates V, Heffner RR Jr. Subcortical arteriosclerotic encephalopathy (Binswanger's disease): computed tomographic, nuclear magnetic resonance, and clinical correlations. *Arch Neurol.* 1985;42:951-959.
14. Masdeu JC, Wolfson L, Lantos G, et al. Brain white-matter changes in the elderly prone to falling. *Arch Neurol.* 1989;46:1292-1296.
15. Hennerici MG, Oster M, Cohen S, et al. Are gait disturbances and white matter degeneration early indicators of vascular dementia? *Dementia.* 1994;5:197-202.
16. Rao SM, Mittenberg W, Bernardin L, et al. Neuropsychological test findings in subjects with leukoaraiosis. *Arch Neurol.* 1989;46:40-44.
17. Schmidt R, Fazekas F, Offenbacher H, Dusleag J, Lechner H. Magnetic resonance imaging white lesions and cognitive impairment in hypertensive individuals. *Arch Neurol.* 1991;48:417-420.
18. Fife TD, Baloh RW. Disequilibrium of unknown cause in older people. *Ann Neurol.* 1993;34:694-702.
19. Tinetti ME, Williams TF, Mayewski R. Fall risk index for elderly patients based on number of chronic disabilities. *Am J Med.* 1986;80:429-434.
20. Brandt T, Steddin S, Eng D, Daroff RB. Therapy for benign paroxysmal positioning vertigo, revisited. *Neurology.* 1994;44:796-800.
21. Katz S, Ford AB, Moskowitz AW, et al. Studies of illness in the aged: the index of ADL: a standardized measure of biological and psychosocial function. *JAMA.* 1963;185:914-919.
22. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist.* 1969;9:179-186.
23. Folstein M, Folstein S, McHugh P. 'Mini-Mental State': a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975;12:189-198.
24. Lezak MD. *Neuropsychological Assessment.* New York, NY: Oxford University Press; 1983.
25. Baloh RW, Langhofer L, Honrubia V, Yee RD. On-line analysis of eye movements using a digital computer. *Aviat Space Environ Med.* 1980;51:563-567.
26. Baloh RW, Yee RD, Honrubia V. Late cortical cerebellar atrophy: clinical and oculographic features. *Brain.* 1986;109:159-180.
27. Shaw NA. Age-dependent changes in central somatosensory conduction time. *Clin Electroencephalogr.* 1992;23:996-1002.
28. Nutt JG, Marsden CD, Thompson PD. Human walking and higher-level gait disorders, particularly in the elderly. *Neurology.* 1993;43:268-279.