

# Association Between Leukoaraiosis and Saccadic Oscillation

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**Objective:** To use an audiovestibular test battery to evaluate patients with leukoaraiosis in order to investigate the relationship between vertigo and dizziness and leukoaraiosis.

**Design:** Retrospective study.

**Setting:** Tertiary university hospital.

**Patients:** A total of 18 elderly patients with vertigo and dizziness and with leukoaraiosis confirmed by magnetic resonance imaging (hereafter, leukoaraiosis group), and another 18 age- and sex-matched patients with vertigo and dizziness but without leukoaraiosis (hereafter, nonleukoaraiosis group) were enrolled in this study.

**Main Outcome Measures:** Each patient underwent a battery of audiovestibular tests, including audiometry and electronystagmography (ENG).

**Results:** In the leukoaraiosis group, ENG examination showed slow pursuit movements in 72% of patients, slowing of saccadic eye movements in 28%, abnormal optokinetic nystagmus test results in 44%, and canal paresis or caloric areflexia in 56% of cases. Compared with the nonleukoaraiosis group, 50%, 17%, 44%, and 61% of cases exhibited nonsignificant differences in slow pursuit movements, slowing of saccadic eye movements, abnormal optokinetic nystagmus test results, and abnormal caloric test results, respectively. However, saccadic oscillation had an occurrence rate of 72% in the leukoaraiosis group in contrast with a 22% rate in the nonleukoaraiosis group, revealing a significant statistical difference.

**Conclusions:** Saccadic oscillations in the ENG examination indicated leukoaraiosis on the magnetic resonance imaging scan, with a sensitivity of 72% and a specificity of 78%. We therefore recommend using ENG examination to screen elderly individuals with leukoaraiosis.

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ON THE BASIS OF GREEK ETYMOLOGY and Hippocratic usage, *leukoaraiosis* is defined as a diminution of density in the white matter, related to a specific type of cerebral ischemia,<sup>1</sup> which has been identified as a low-density area on a computed tomographic scan or high signal intensity on a T2-weighted magnetic resonance imaging (MRI) scan. Although the pathogenesis remains inconclusive, leukoaraiosis has been considered to be the result of ischemic brain injury originating from hypoperfusion in the distal deep arterial or arteriolar territories.<sup>2</sup> The effects of aging and of various vascular risk diseases (eg, stroke and heart disease) have been found to have a relationship with leukoaraiosis.<sup>3,4</sup> Because higher blood pressure is associated with white matter hypertensity and brain atrophy, patients with higher systolic blood pressure are more likely to develop leukoaraiosis.<sup>5,6</sup>

Clinical manifestations are of subtle onset, with a general disabling nature and causing personality change without prominent focal neurological signs. Some indi-

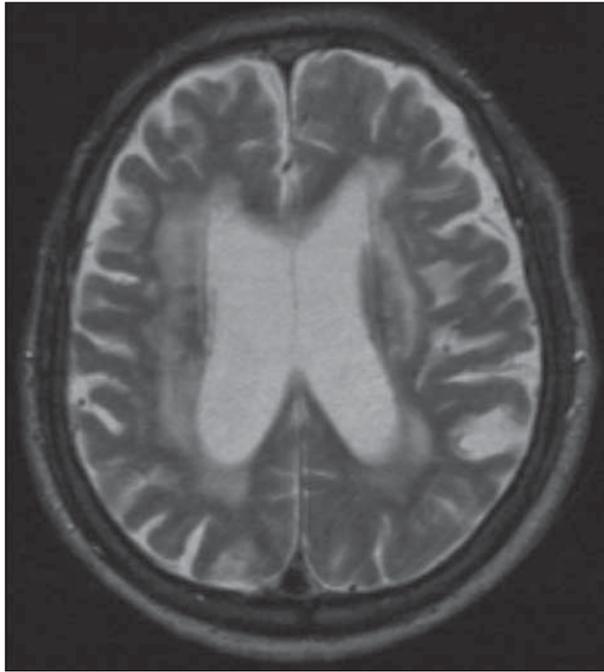
viduals remain free of symptoms for years, whereas others develop gait disorder, a tendency to fall, cognitive impairment, dementia, lacunar stroke, or parkinsonism features.<sup>7</sup> Recently, more and more elderly patients presenting with vertigo, dizziness, unsteady gait, or disequilibrium visit neurologists for treatment of their balance problems, and findings from MRI scans demonstrate leukoaraiosis. Whether leukoaraiosis correlates with vertigo and dizziness in the elderly population remains unexplored. Hence, the aim of this study was to use audiovestibular test batteries to evaluate patients with leukoaraiosis to investigate that relationship.

## METHODS

### PATIENTS

Of 21 patients with leukoaraiosis whose diagnosis was confirmed by MRI scan, a total of 18 with vertigo and dizziness (hereafter, the leukoaraiosis group) were enrolled in this study; 3 patients with unsteady gait only were excluded. Six of the patients were men, and 12 were women; their mean age was 68 years

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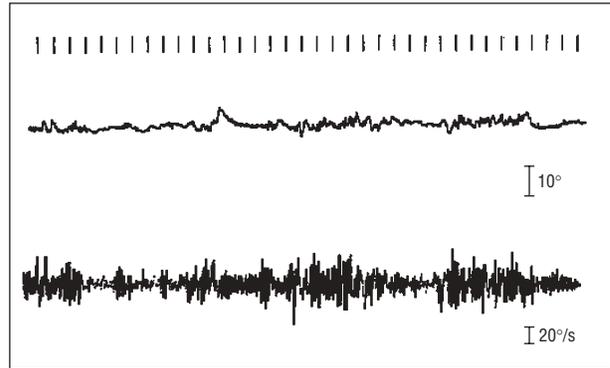
**Figure 1.** Findings from a T2-weighted magnetic resonance imaging scan demonstrates high signal intensity in bilateral periventricular areas, consistent with a diagnosis of leukoaraiosis.

(range, 59-75 years). Seventeen patients (94%) had underlying systemic diseases such as hypertension (15 [83%]), dyslipidemia (5 [28%]), coronary artery disease (5 [28%]), and diabetes mellitus (4 [22%]) (8 patients [44%] had multiple disorders). We took a detailed medical history from each patient, and their blood pressure measurement was taken; each patient then underwent a battery of tests, including physical and neurological examinations, blood chemistry profile, audiometry, electronystagmography (ENG), and MRI scan.

For comparison, another group of 18 age- and sex-matched elderly patients admitted to our ward owing to acute vertigo was also recruited (hereafter, the nonleukoaraiosis group). The findings from MRI scans of these patients did not demonstrate leukoaraiosis, and each patient underwent the same battery of audiovestibular tests as did the leukoaraiosis group.

### DIAGNOSTIC TESTING

The ENG (model OK-5; Nagashima, Tokyo, Japan) examination consisted of recording the spontaneous nystagmus first, followed by pursuit, saccade, optokinetic nystagmus (OKN), and caloric tests. The pursuit test was performed while the subject was seated with the head mechanically immobilized. The subject was asked to follow a moving target at a distance of 100 cm moving in a clockwise circle with a radius of 25.5 cm at a constant rate of 30° per second. The horizontal component of eye movements was represented in a sinusoidal curve of 0.33 Hz with a maximum displacement of 20° from the center. The saccade test was induced by a target moving in steps of 30° amplitude, with a 2-second interval between jumps. The OKN test was triggered by a horizontal optokinetic stimulation using a revised Jung-type Ohm drum for stimulation, at an angular acceleration/deceleration rate of  $\pm 4^\circ/s^2$ . A bithermal caloric test was performed using 20 mL of cold tap water to irrigate the external ear canal for 20 seconds during ENG recording. Canal paresis was defined as a greater than 25% difference between maximum slow-phase velocity measurements for each ear compared with the sum of slow-phase velocities from each



**Figure 2.** Electronystagmographic recordings reveal saccadic oscillation, that is, rapid involuntary, repetitive, conjugate saccadic eye movements. The upper trace is time based at 1 tick mark per second. The middle trace is the horizontal eye movement, and the lower trace is the differentiated horizontal eye movement, indicating eye velocity.

ear. If cold water failed to elicit caloric response, the subject underwent caloric testing with ice water irrigation (using 10 mL of water that was 0°C) to further confirm the presence of caloric areflexia.

We performed MRI studies using the Magnetom Plus 1.5T (Siemens; Erlangen, Germany) on a superconducting 1.5-T MRI system with a slice thickness of 4 mm. The T1-weighted, T2-weighted, or proton density images on either coronal or axial planes were investigated.

Abnormal rates between the leukoaraiosis and the nonleukoaraiosis groups in terms of hearing and vestibular function tests were compared by Fisher exact test.  $P < .05$  indicates a significant difference.

### TREATMENT

All patients in the leukoaraiosis group were treated with plasma expander (eg, hydroxyethyl starch) at a dosage of 1.0 L daily for 3 consecutive days. Subsequently, oral medication such as ginkgo biloba (40 mg), multiple vitamins (1 tablet), and a mild tranquilizer (oxazolam, 10 mg) were given twice daily for at least 3 consecutive months. Each patient was regularly followed up once a month at our vertigo clinic to assess the compliance of the patient when receiving multiple drugs. The evaluation of the treatment efficacy was based on both subjective vertigo sensation (by the patient) and objective nystagmus observation, as detected by the spontaneous and/or provoked nystagmus by vestibular function test.<sup>8</sup>

This study was approved by our institutional review board, and each patient provided informed consent.

### RESULTS

Clinical manifestation of symptoms in the leukoaraiosis group (**Figure 1**) consisted of rotatory vertigo in 13 (72%), nausea and vomiting in 10 (56%), tinnitus in 9 (50%), unstable gait in 9 (50%), wheelchair dependency in 7 (39%), ataxia in 4 (22%), and problems with falling in 3 (17%). The maximum mean systolic blood pressure during hospitalization was 147 mm Hg (range, 120-210 mm Hg).

Findings from audiometry tests revealed high-tone sensorineural hearing loss in 25 ears (69%), flat-type hearing loss in 4 ears (11%), low-tone hearing loss in 2 ears (6%), total deafness in 2 ears (6%), and normal hearing

**Table 1. Vestibular Abnormalities in 18 Patients With Vertigo and Dizziness With Leukoaraiosis**

Patient/ Sex/Age, y	Pursuit Test, 13 Patients (72%)	Saccade Test, 5 Patients (28%)	OKN Test, 8 Patients (44%)	Caloric Test (R/L), 10 Patients (56%)	Saccadic Oscillation, 13 Patients (72%)
1/F/74	Abn	N	N	N/N	-
2/F/65	Abn	Abn	N	N/N	+
3/F/73	Abn	N	N	N/N	+
4/F/71	Abn	Abn	N	N/N	+
5/M/75	N	N	N	N/N	-
6/M/65	Abn	Abn	Abn	N/-	+
7/F/75	N	N	N	-/CP	+
8/F/62	Abn	N	N	N/N	+
9/F/61	N	N	N	CP/N	-
10/M/63	Abn	N	Abn	-/-	+
11/F/66	Abn	N	N	N/-	-
12/F/69	Abn	N	Abn	N/N	+
13/F/70	Abn	Abn	N	-/-	+
14/M/75	N	N	Abn	CP/CP	+
15/F/70	Abn	N	Abn	CP/N	+
16/M/59	Abn	N	Abn	-/N	+
17/F/67	N	N	Abn	N/CP	+
18/M/69	Abn	Abn	Abn	N/N	-

Abbreviations: Abn, abnormal; CP, canal paresis; L, left; N, normal; OKN, optokinetic nystagmus; R, right; -, absent; +, present.

**Table 2. Vestibular Abnormalities in 18 Patients With Vertigo and Dizziness Without Leukoaraiosis**

Patient/ Sex/Age, y	Pursuit Test, 50% Abnormal Rate	Saccade Test, 17% Abnormal Rate	OKN Test, 44% Abnormal Rate	Caloric Test (R/L), 61% Abnormal Rate	Saccadic Oscillation, 22% Abnormal Rate
19/F/72	Abn	N	N	N/N	+
20/F/68	Abn	N	N	CP/N	+
21/F/65	N	Abn	N	CP/N	-
22/F/67	Abn	N	N	CP/CP	-
23/M/75	N	Abn	Abn	N/-	-
24/M/59	N	N	N	N/N	+
25/F/66	N	N	Abn	CP/CP	+
26/M/67	N	N	N	CP/-	-
27/F/66	Abn	N	N	N/CP	-
28/M/65	N	N	N	CP/CP	-
29/M/66	Abn	N	Abn	N/N	-
30/M/71	N	N	N	CP/N	-
31/F/59	Abn	N	N	N/CP	-
32/F/73	Abn	Abn	Abn	N/N	-
33/F/66	N	N	Abn	N/N	-
34/F/67	Abn	N	Abn	-/N	-
35/F/65	N	N	Abn	N/N	-
36/F/71	Abn	N	Abn	N/N	-

Abbreviations: Abn, abnormal; CP, canal paresis; L, left; N, normal; OKN, optokinetic nystagmus; R, right; -, absent; +, present.

in 3 ears (8%). Findings from the ENG examination showed slow pursuit movements in 13 patients (72%), slowing of saccadic eye movements in 5 patients (28%), abnormal OKN test findings in 8 patients (44%), abnormal caloric responses (eg, canal paresis or caloric areflexia) in 10 patients (56%), and saccadic oscillation (**Figure 2**), including lightning eye movements or opsoclonus, in 13 patients (72%) (**Table 1**).

In the nonleukoaraiosis group, abnormalities were found in 72% of findings from the hearing test (13 patients), 50% of findings from the pursuit test (9 patients), 17% of findings from the saccade tests (3 patients), 44% of findings from the OKN tests (8 patients), 61% of findings from the caloric test (11 patients), and 22% of

findings from the saccadic oscillations (4 patients) (**Table 2**). Comparison between the leukoaraiosis and nonleukoaraiosis groups revealed nonsignificant differences in terms of the hearing ( $P = .40$ ), pursuit ( $P = .31$ ), saccade ( $P = .69$ ), OKN ( $P > .99$ ), and caloric ( $P > .99$ ) tests (Fisher exact test). However, significant differences between the 2 groups existed in the occurrence of saccadic oscillation ( $P < .007$ , Fisher exact test) (**Table 3**). Thus, saccadic oscillations in ENG examination indicated leukoaraiosis, with a sensitivity of 72% and a specificity of 78%.

Except for 8 patients from our clinic who were lost to follow-up owing to reasons such as development of cancer, stroke, parkinson disease, or polyneuropathy, the

**Table 3. Comparison of Vestibular Abnormalities in Patients With Vertigo and Dizziness With vs Without Leukoaraiosis\***

Group, No. of Patients	Patients With Abnormalities, %				
	Pursuit Test	Saccade Test	OKN Test	Caloric Test	Saccadic Oscillation*
With leukoaraiosis, 18	72	28	44	56	72
Without leukoaraiosis, 18	50	17	44	61	22

Abbreviation: OKN, optokinetic nystagmus.

\*The *P* value for saccadic oscillation was  $<.05$ ; for the other tests the *P* value was nonsignificant.

remaining 10 patients were regularly followed up at our vertigo clinic for more than 6 months, with a median duration of follow-up of 7.2 months. One year after presentation, the vertigo and imbalance symptoms of 9 of the 10 patients had resolved.

### COMMENT

Next to aging, systemic disease (eg, hypertension, coronary artery disease, or diabetes mellitus) is an additional risk factor for the development of leukoaraiosis.<sup>9</sup> The cerebral white matter receives most of its blood supply through long penetrating arteries originating from the pia network and ventriculofugal vessels arising from subependymal arteries.<sup>2</sup> Aging and chronic hypertension share a common substrate of arteriosclerosis that occurs on the small penetrating arteries and arteriole of the white matter. In the study described herein, advanced age (mean, 68 years) associated with a higher rate (83%) of hypertension indicated that ischemia leads to leukoaraiosis. Arteriosclerosis, almost always detected with areas of leukoaraiosis, may be one of the factors responsible for altering the blood supply to the white matter, and this vascular alteration may result in either localized ischemic areas of necrosis and cavitation (ie, lacunes) or diffuse rarefaction (ie, leukoaraiosis). Because leukoaraiosis is frequently combined with lacunar infarct on MRI findings, the term *ischemic leukoaraiosis* is defined as a combination of radiological leukoaraiosis and clinical lacunar stroke, excluding those of potential large vessel disorders (eg, cortical or subcortical infarcts) larger than 15 mm in maximum diameter.<sup>7</sup>

The MRI scans of some elderly patients with vertigo and dizziness frequently demonstrated leukoaraiosis at bilateral periventricular areas (Figure 1). Although leukoaraiosis is a specific type of cerebral ischemia, it remains unclear whether vertigo and dizziness are due to ischemic change extending into the posterior cranial fossa. Therefore, audiovestibular test results were analyzed.

Audiometry findings revealed sensorineural hearing loss in 94% and 72% of the leukoaraiosis and nonleukoaraiosis groups, respectively, exhibiting a nonsignificant difference ( $P>.05$ ; Fisher exact test). Thus, audiological measurements cannot be used as an indicator for leukoaraiosis because multiple factors (eg, aging, environmental, or genetic factors) can alter the hearing status in elderly individuals.

In the ENG examination for oculomotor movements, the pursuit test is used to investigate the occipi-

tomesencephalic system (eg, cerebral cortex areas 17, 18, and 19; internal corticotectal tract; superior colliculus; mesencephalic tegmentum; the oculomotor; trochlear; and abducent nuclei). The saccade test evaluates the pathways involving the cerebral cortex area 8, the corticobulbar tract, and the paramedian pontine reticular formation,<sup>10</sup> whereas the OKN test is related to area 8 of the frontal lobe, area 18 of the occipital lobe, and their projecting fibers.<sup>11</sup> The fact that the leukoaraiosis and nonleukoaraiosis groups did not differ significantly in these regards means that aging effect rather than ischemic change played a major role in the development of oculomotor abnormalities.

The disequilibrium of aging, termed *presbyastasis*,<sup>12</sup> could occur in the vestibular sensory cells, vestibular nerve, Scarpa ganglion, or cerebellum. However, Mallinson and Longridge<sup>13</sup> stated that caloric responses do not reflect anatomically documented age-related senescence of the vestibular system. The discrepancy between morphological and functional changes is possibly due to central adaptive mechanism or redundancy.<sup>14</sup> In the current study, abnormal caloric responses (eg, caloric areflexia or canal paresis) presented as 56% and 61% of occurrences in the leukoaraiosis and nonleukoaraiosis groups, respectively, showing a nonsignificant difference (Table 3). Therefore, caloric response is unrelated to leukoaraiosis because the vestibulo-ocular reflex pathway did not transit the periventricular regions.

Conversely, saccadic oscillations (Figure 2) (eg, lightning eye movements and opsoclonus) presented as 72% and 22% of occurrences in the leukoaraiosis and nonleukoaraiosis groups, respectively, exhibiting a statistical difference (Table 3). Lightning eye movement is defined as horizontal saccadic eye movements in bursts of 3 to 4 movements lasting less than 0.5 seconds, generally 3° to 5° in amplitude, with a brief stationary period between successive jerks,<sup>15,16</sup> whereas opsoclonus is a dyskinesia consisting of involuntary arrhythmic, chaotic, multidirectional saccades without intersaccadic intervals.<sup>17</sup>

The mechanism of saccadic oscillation is considered to be a selective loss of a specific neuronal population, namely, pause cells, which is usually caused by the brainstem dysfunction.<sup>18</sup> Conversely, brainstem lesion evokes another inappropriate, repetitive, alternating discharge of burst neurons. The basal ganglia control these saccade-related burst neurons in the superior colliculus, via prevention of unwanted reflexive saccades to stimuli, and subsequently aid in steady fixation.<sup>19</sup> Although the frontal eye fields and the superior colliculus also provide the

major descending input to the brainstem saccadic burst generators, the saccadic burst neurons and the nuclei of the extraocular muscle motor neurons remain relatively unchanged during an individual's lifespan.<sup>20</sup> Hence, saccadic oscillation is attributable to the loss of control by basal ganglia, compatible with microangiopathy of bilateral basal ganglia on findings from the MRI scan. Put another way, saccadic oscillation can be used to reflect leukoaraiosis, with a sensitivity of 72% and a specificity of 78%. Because leukoaraiosis is regarded as an intermediate surrogate of stroke,<sup>21</sup> we therefore recommend using ENG to detect this kind of ischemic change.

Because of the ischemic nature of leukoaraiosis, an intravenous plasma expander (eg, hydroxyethyl starch) was administered to the patients to enhance the microvasculature.<sup>22</sup> Subsequently, oral medication was given for at least 3 consecutive months. The rationale for the multidrug treatment in patients with vertigo and dizziness with leukoaraiosis was as follows: ginkgo biloba improves blood flow and impeding platelet aggregation, a multiple vitamin prevents deficiencies in elderly individuals, and a minor tranquilizer serves as a vestibular suppressant by down-regulating vestibular excitability. Although Inzitari<sup>21</sup> reported that no intervention is known to be capable of controlling leukoaraiosis, and, to our knowledge, no proof exists that treating leukoaraiosis prevents stroke, alleviation of vertigo and unsteady gait can be achieved in 9 of 10 patients with leukoaraiosis after treatment with antivertigo medication.

In conclusion, saccadic oscillations in ENG examination indicated the presence of leukoaraiosis on MRI scans, with a sensitivity of 72% and a specificity of 78%. We therefore recommend using ENG examination for screening elderly individuals with leukoaraiosis.

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**Author Contributions:** Dr Young had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Young. *Acquisition of data:* Wu. *Drafting of the manuscript:* Wu. *Critical revision of the manuscript for important intellectual content:* Young. *Statistical analysis:* Wu. *Administrative, technical, and material support:* Young. *Study supervision:* Young.

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