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Leukoencephalopathy in Normal and Pathologic Aging: 1. CT of Brain Lucencies

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Central white matter lucencies are commonly seen in CT scans of elderly patients. Reports in the literature have implicated demyelination due to subcortical vascular disease (Binswanger disease) as the cause of these lucencies. Binswanger disease, however, is thought to be rare. Because of this apparent discrepancy we decided to determine the incidence and to attempt to define the clinical significance of the CT white-matter changes in a study population at New York University Medical Center. The studies of 275 normal and demented subjects, ages 23 to 85 years, were reviewed. All subjects received neurologic, psychiatric, and medical evaluation, formal psychometric evaluation of their cognitive status, and a CT scan. CT scans were evaluated for the presence and severity of white-matter changes (leukoencephalopathy). The incidence and severity of white-matter changes increased significantly with age ($p < 0.01$). Leukoencephalopathy was consistently more common in demented patients than in normal subjects, but the difference was not statistically significant, and the severity of the leukoencephalopathy was not related to the severity of dementia ($p > 0.05$). Five patients (ages 74 to 95 years) with a clinical diagnosis of Alzheimer disease who had CT evidence of lucencies were examined at autopsy. Neuropathology demonstrated extensive changes of Alzheimer disease in one brain and mild-to-moderate changes in the other four brains; areas of white-matter rarefaction were present in all brains, with microscopic evidence of arteriolar hyalinization. This study demonstrates that leukoencephalopathy is strongly related to the aging process and is seen in both "normal" and cognitively impaired individuals who have no other evidence of vascular disease. White-matter lucencies are not necessarily associated with dementia, but their increased incidence in Alzheimer disease patients and the neuropathologic results suggest that their presence may represent a risk factor potentiating the effects of Alzheimer disease.

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Improved contrast resolution of currently available CT scanners has resulted in the frequent demonstration of white-matter lucencies in the brains of elderly patients. Evidence to date based on limited autopsy series [1-6] suggests that this leukoencephalopathy reflects the changes of subcortical vascular encephalopathy or Binswanger disease. This entity, originally described in 1894 [7], is thought to be a rare occurrence associated with stroke, hypertension, and dementia [3, 5]. Binswanger himself identified only eight cases in 11 years. The pathologic changes [3, 5] include patches of demyelination and cyst formation associated with hyalinization of medullary arterioles. We have noted that CT white-matter lucencies are commonly present in our study patients with clinically diagnosed Alzheimer disease (senile dementia of the Alzheimer type, or SDAT) who have no history of hypertension or stroke, as well as in normal elderly subjects. We therefore undertook clinical, radiologic, and neuropathologic studies of normal and demented subjects in order to determine the incidence of CT white-matter lucencies and to attempt to define the clinical and pathologic significance of these changes.

Subjects and Methods

This report is based on the findings from 275 subjects, consisting of cognitively impaired

patients and normal volunteer controls. All impaired subjects are participants in the New York University Geriatric Study and Treatment program. Normal controls were derived in part from the spouses of the impaired group. All subjects received medical, neurologic, psychiatric, and neuropsychological evaluations and a CT scan. Following this screening protocol and using the exclusion criteria described below, all subjects that were diagnosed as normal or as presumed Alzheimer disease (SDAT) were selected for study.

The control subjects were from two cognitively normal groups: an elderly group, consisting of 89 subjects, 44 men and 45 women (mean age, 69.5 years), and a young group, consisting of 35 men (mean age, 25.0 years).

The Alzheimer subjects consisted of 151 demented, elderly patients, 88 women and 63 men (mean age, 72.5 years) who were diagnosed clinically as having SDAT.

All subjects with history of stroke or with neurologic or CT evidence of stroke were excluded. Subjects with hypertensive and/or cardiac disease requiring medication other than diuretic drugs were excluded. Also excluded were subjects with diabetes requiring treatment with insulin or oral medication. Those with diabetes under dietary control were not excluded from the study.

Medical-Neurologic Evaluation

The clinical evaluation included history and physical examination, routine blood and urine analyses, and a determination of blood pressure. Subjects with blood pressure of 150 systolic over 90 diastolic or less were considered normotensive. Subjects with systolic or diastolic pressure above these levels were considered hypertensive. After complete neurologic evaluation the presence or absence of gait disturbance was assessed and recorded by the examining neurologist. Historic and physical evidence of heart disease, diabetes, or peripheral vascular disease was also tabulated as either present or absent.

Psychometric Evaluation of Cognitive Status

Each study subject received a psychiatric and neuropsychological test battery, which has been in use in our laboratory for 10 years. This examination included the Global Deterioration Scale (GDS) [8] and the Guild Memory Test. The Guild includes a measure of vocabulary, immediate and delayed recall of paragraphs, paired associates, digit span, and memory for designs. A score on the GDS that indicated moderate to severe symptomatology (GDS >4) was required for a patient to be included in the dementia group.

CT Examination

CT scans were obtained for all patients and normal controls on the General Electric 8800 CT scanner (General Electric, Milwaukee, WI). Scans were obtained without intravenous contrast administration with the scanning plane parallel to the canthomeatal line. Scan parameters were mA = 200 to 320, scan time = 9.6 sec, slice thickness = 10 mm. Hard-copy images were obtained at constant window (80 H) and level (40 H) settings.

Subjective assessment for the presence or absence of lucency was done independently by two observers who were unaware of the patients' clinical status. Subsequently, the observers evaluated the severity of leukoencephalopathy with a seven-point rating scale using hard-copy images. Scans were rated as demonstrating no, minimal, mild, mild-to-moderate, moderate, moderate-to-severe, or severe leukoencephalopathy. "Minimal" implied faintly visualized lucencies, usually in the white matter anterior and lateral to the frontal horns or,

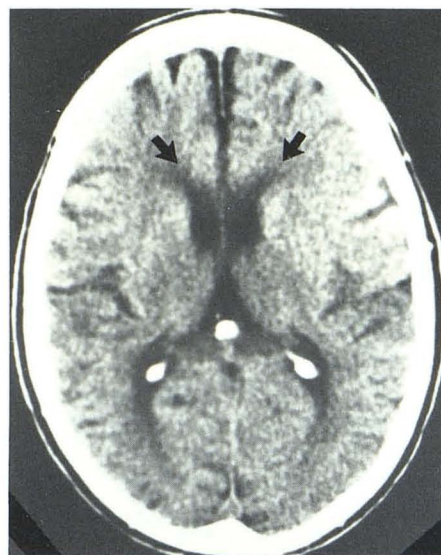


Fig. 1.—CT of mild leukoencephalopathy in 83-year-old woman. Faint lucencies (arrows) involve white matter adjacent to frontal horns.

occasionally, in the peritrigonal areas. "Mild" (Fig. 1) implied lucencies occupying less than one-third of the visualized white matter of the frontal and peritrigonal areas. "Moderate" implied involvement of approximately one-half of the visualized white matter. "Severe" implied involvement of virtually all visualized white-matter regions (Fig. 2).

Neuropathology

As part of a larger ongoing neuropathology study of Alzheimer disease, postmortem examinations were performed on five patients with clinical diagnosis of Alzheimer disease who had CT evidence of leukoencephalopathy prior to death. The brains were fixed in 10% formalin for 3 weeks, in accordance with standard procedure, and then sectioned in the coronal plane. Microscopic examination of multiple brain samples was routinely performed. This included the neocortex with subcortical and deep white matter of the frontal, temporal, parietal, and occipital lobes. Also included for study were the basal ganglia, the nucleus basalis of Meynert, the hippocampi, the hypothalamus, the thalami, the lower brainstem, and the cerebellum. In addition, using the CT for localization, we sampled the specific sites of leukoencephalopathy. All sections were routinely stained with hematoxyline and eosine. Luxol-fast-blue/PAS and silver impregnation methods were used in the study of selected blocks.

Results

Incidence of Leukoencephalopathy

The overall incidence of leukoencephalopathy in the two control groups and the Alzheimer disease group is given in Table 1. These figures indicate no lucencies in the young control subjects and also suggest a higher incidence of lucencies in the Alzheimer disease group when compared with the elderly control subjects. For both the elderly control group and the Alzheimer disease group a significantly increased

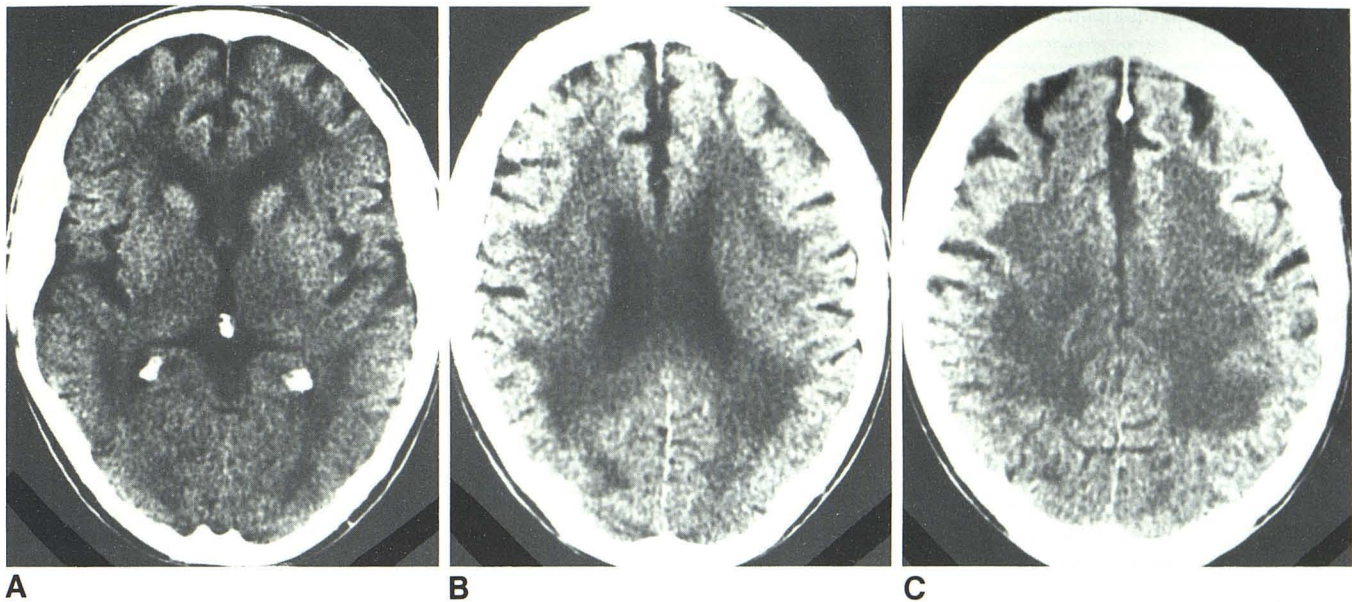


Fig. 2.—CT of severe leukoencephalopathy in 70-year-old man. Virtually all visualized white matter demonstrates lucencies at basal ganglia (A), ventricular (B), and centrum (C) levels.

incidence of lucencies was found with increasing age. With the subjects divided into two age groups (55–69 and 70–85 years) for determining the presence or absence of lucencies, we found that in the Alzheimer patients the incidence of lucency increased from 18% in the 55–69 age group to 35% in the 70–85 age group (chi square = 4.53 $p < 0.05$) (Fig. 3). The incidence of leukoencephalopathy among normal older patients increased from 7% in the 55–69 age group to 24% in the 70–85 age group (chi square = 5.21 $p < 0.05$). For the Alzheimer patients as compared with the normal controls (Fig. 3), there was a nonsignificant trend toward a higher incidence of leukoencephalopathy for both the younger (chi square = 2.75 $p > 0.05$) and the older (chi square = 1.69 $p > 0.05$) groups. These results indicate that the incidence of leukoencephalopathy increases with increasing age in both normal subjects and in patients with presumed Alzheimer disease.

The anatomic distribution of lucencies in the Alzheimer group is shown in Table 2. These data indicate that involvement of the frontal white matter is present in 86% of cases with lucencies.

Clinical Correlates of Leukoencephalopathy

For both the normal subjects and patients with presumed Alzheimer disease, the frequency of various clinical param-

eters is tabulated in Table 3. Note that the incidence of hypertension in the normal population with leukoencephalopathy was 57% whereas only 25% of normals without leukoencephalopathy were hypertensive. Thus the presence of lucencies is twice as frequent in hypertensive normals. This was not the case in the Alzheimer patients, among whom 22% without lucencies were hypertensive and 24% with lucencies were hypertensive.

The presence of leukoencephalopathy was not associated with a significant increase in the associated incidence of heart disease, peripheral vascular disease, or diabetes.

We also found that leukoencephalopathy was associated with a significantly increased incidence of gait impairment in the Alzheimer disease patients.

Table 4 shows a correlation between leukoencephalopathy severity ratings and the above medical parameters and age for both normal and Alzheimer groups combined. The leukoencephalopathy rating (severity) showed no relationship to the degree of dementia. Severity of leukoencephalopathy was

TABLE 1: Incidence of CT White-Matter Lucencies

Group	No. of Cases	Mean Age (SD)	No. of Lucencies (%)
Young normal	35	25.0 (± 2.0)	0 (0)
Old normal	89	69.4 (± 6.5)	14 (16)
Alzheimer	151	72.6 (± 7.5)	45 (30)

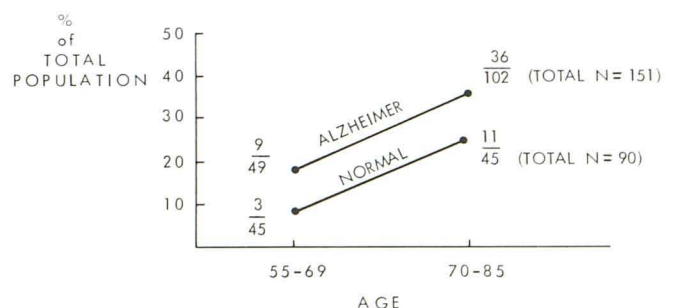


Fig. 3.—CT leukoencephalopathy; percent of affected normal individuals and Alzheimer's patients by two age groups.

TABLE 2: Percent Distribution of CT Lucencies in Alzheimer Group (*n* = 45)

Frontal	39
Frontal and peritrigonal	32
Peritrigonal	14
Diffuse	15

significantly related to age and also to the presence or absence of gait impairment. Thus, the older the subject, the greater the likelihood the leukoencephalopathy would be severe and the subject's gait would be impaired.

Neuropathology

Neuropathologic findings from five patients clinically diagnosed as having Alzheimer disease are summarized in Table 5. These patients had CT evidence of lucencies that ranged in severity from mild to severe. Their ages at death ranged from 74 to 95 years and all subjects were severely demented with GDS ratings of either 6 or 7. At autopsy, white-matter rarefaction and focal spongy changes were present in all cases. On histologic examination, all brains demonstrated typical features of subcortical vascular disease; that is, demyelination, hyalinization of medullary arterioles, and cystic degeneration corresponding to the white-matter lucencies demonstrated by CT. Arteriolar changes ranged from moderate to severe.

Alzheimer changes were also present at postmortem in all five subjects. The distribution and severity of senile plaques and neurofibrillary tangles are given in Table 5. One patient (subject 4), a 75-year-old woman with severe CT lucencies at postmortem (Fig. 4) showed extensive evidence of Alzheimer disease as well as extensive concomitant white-matter changes. The patient had had long-standing hypertension. The brain after fixation weighed 1200 grams. The white matter of the centrum semiovale of the anterior two-thirds of both frontal lobes was soft and finely porous. Both hippocampal formations showed approximately 50% reduction in size. Microscopically, arteriolar hyalinization was moderate. No infarcts or lacunes were present. A single 2-mm hemorrhage, which was assumed to be of hypertensive origin, was found in the inferior extremity of the right postcentral gyrus. Alzheimer changes consisted of numerous plaques and tangles in the neocortex. Tangles were also seen in the nucleus basalis and hypothalamic nuclei and in the upper and lower brainstem.

In the other four autopsied brains, Alzheimer changes ranged from mild (subjects 5 and 1) to moderate (subjects 2 and 3). In subjects 5 and 1, a discordance is suggested between the degree of dementia, which was severe, and the severity of Alzheimer changes at autopsy, which was mild (Table 5). For example, in subject 5, a 74-year-old woman, only a few plaques and tangles were present in the cortex with rare tangles in the nucleus basalis. CT leukoencephalopathy was severe and corresponded to the pathologic findings of moderate-to-severe arteriolar hyalinization and moderate-

TABLE 3: Percent Incidence of Medical Parameters

	Without Lucencies	With Lucencies	Chi Square
Elderly normals	(<i>n</i> = 75)	(<i>n</i> = 14)	
Hypertension	25	57	4.25*
Heart disease	14	8	0.02
Peripheral vascular	15	15	0.00
Diabetes	8	0	0.22
Gait impairment	3	8	0.00
Alzheimer patients	(<i>n</i> = 106)	(<i>n</i> = 45)	
Hypertension	22	24	0.05
Heart disease	18	16	0.05
Peripheral vascular	16	24	1.00
Diabetes	6	0	1.07
Gait impairment	20	45	6.81*

* *p* < 0.05

TABLE 4: Severity Rating of Leukoencephalopathy vs Clinical Measures, Pearson Product Correlations: Normal Subjects and Alzheimer Patients Combined (*n* = 58)

Age	0.36**
Mental status (GDS)	0.09 (NS)
Hypertension	0.09 (NS)
Heart disease	-0.16 (NS)
Peripheral vascular	-0.04 (NS)
Gait impairment	-0.32*

** *p* < 0.01

* *p* < 0.05

Note.—GDS = Global Deterioration Scale; NS = nonsignificant.

to-severe leukoencephalopathy. The white matter was finely porous with ill-defined, 4- to 6-mm cysts present bilaterally.

Discussion

Subcortical vascular encephalopathy was recently reported at autopsy [5] in only 3.8% of patients over the age of 60. We report CT evidence of leukoencephalopathy in 30% of our patient population with clinical diagnosis of Alzheimer disease and in 16% of normal, age-matched controls. We excluded all subjects who had historic, physical, or CT evidence of stroke. The increased incidence of lucencies in the Alzheimer group, though not statistically significant, does raise the possibility that the subjects are predisposed to the dementing process of Alzheimer disease, perhaps causing earlier manifestation of the dementia or more severe dementia than in patients without lucencies. This hypothesis is supported by the neuropathologic findings. All five autopsy patients had been severely demented prior to death. The neuropathologic examinations demonstrated typical features of subcortical vascular disease; that is, hyalinization of small arteries and arterioles and demyelination, but only one brain exhibited extensive plaque and neurofibrillary tangle formation typical of severe Alzheimer disease. Presumably the patient who had extensive changes of Alzheimer disease would have had a clinical presentation of dementia even without the extensive white-matter changes, which were also present. A

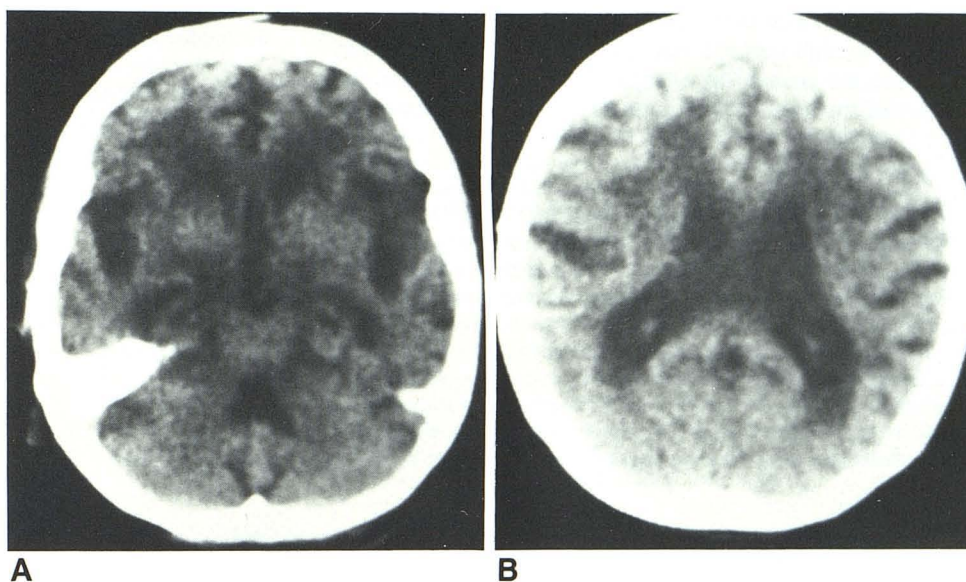
TABLE 5: Neuropathology Cases

Case No.	Age Gender	Clinical Severity of Dementia	Alzheimer Plaques (NEO/HIP)	Changes in Neurofibrillary Tangles (NEO/HIP)	CT Lucencies
1	95 M	Severe	Mild/Mild	Minimal/Mild	Mild
2	79 M	Severe	Moderate/Moderate	Minimal/Mild	Minimal
3	82 F	Severe	Moderate/Normal	Moderate/Normal	Minimal
4*	75 F	Severe	Moderate/Moderate	Minimal/Moderate	Severe
5*	74 F	Severe	Minimal/Minimal	Normal/Mild	Severe

* Hippocampal cell loss was severe (estimated 40–50%).

Note.—NEO = neocortex; HIP = hippocampus. All subjects prior to death were rated GDS (Global Deterioration Scale) 6 or 7. 6 implies the subject required assistance and had difficulty communicating. 7 implies loss of all verbal and psychomotor abilities. At postmortem, all subjects demonstrated moderate to severe white-matter changes (see text). For Alzheimer changes, minimal = occasional or rare lesions; mild = scattered lesions; moderate = lesions regularly seen. For CT, minimal = faint lucencies; mild = definite lucencies involving less than one-third of white matter; severe = diffuse involvement of virtually all white matter.

Fig. 4.—CT of neuropathology case 4, obtained 2 months before death. Coexistent Alzheimer disease and leukoencephalopathy; 75-year-old chronically hypertensive, demented woman. **A**, Low basal ganglionic level. **B**, Ventricular body level. At postmortem, both white-matter and Alzheimer changes were found to be extensive.



discrepancy is suggested in two subjects (1 and 5, Table 5) between the severity of Alzheimer disease changes and the degree of dementia. At autopsy, subject 5, a 74-year-old woman, showed only mild evidence of Alzheimer disease and moderate-to-severe leukoencephalopathy. In view of this patient's clinically severe dementia, it is postulated that the white-matter disease contributed to the severity of the dementia. A similar effect is suggested in subject 1, who was a severely demented 95-year-old man. At postmortem, there were mild Alzheimer changes and evidence of moderate white-matter changes. Therefore, in these two cases the presence of leukoencephalopathy may have resulted in the appearance of dementia earlier or with greater severity than if leukoencephalopathy were not present.

An analysis of the medical profiles of all subjects revealed that the lucencies were associated with double the incidence of hypertension in normal individuals but not in the Alzheimer group. We postulate that this apparently unexpected result most likely reflects an inability of the elderly Alzheimer patients to tolerate hypertension superimposed on leukoencephalopathy and Alzheimer disease. Thus, many patients with this

combination may have been either too disabled to participate in the research program or may have sustained a stroke and therefore were excluded from the study. Seventy-six percent of the Alzheimer patients with lucencies and 43% of the normal subjects with lucencies were normotensive. The incidence is higher than that reported by Goto et al. [3], who noted that only two of 10 autopsied patients with diffuse white-matter disease had been normotensive.

The increased incidence of gait impairment in the patients with Alzheimer disease and leukoencephalopathy is also of interest. Alzheimer patients without lucencies, by virtue of their disease alone, showed more than double the incidence of gait impairment (20%) seen in normal patients. That incidence was again doubled if leukoencephalopathy was also present.

Summary

The studies of 275 normal and cognitively impaired subjects with presumed Alzheimer disease were reviewed. CT evi-

dence of leukoencephalopathy was commonly seen in pathologic as well as normal aging. The incidence and severity of leukoencephalopathy increased with age and was especially evident past the age of 70. Leukoencephalopathy was commonly present in the absence of hypertension, diabetes, or cardiac disease. Leukoencephalopathy was more common in patients with presumed Alzheimer disease, showing a nonsignificant trend when compared with normal subjects; leukoencephalopathy severity was *not* related to the degree of dementia. The presence of CT lucencies was associated with double the incidence of hypertension in normal subjects and more than double the incidence of gait impairment in patients with Alzheimer disease. Neuropathologic evidence, including our own study of lucency cases, indicates that CT leukoencephalopathy represents demyelination in association with subcortical vascular disease. The presence of leukoencephalopathy, though perhaps not itself causing dementia, may potentiate the dementing effects of Alzheimer disease and may therefore be a risk factor for dementing disorders.

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