Clinical features of leuko-araiosis

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Abstract

Objective—To study the clinical features of leuko-araiosis.

Methods—Age matched groups of patients with a CT finding of pure leuko-araiosis ($n = 26$) and a control group with a normal CT finding ($n = 26$) were formed (mean ages 78.6 (SD 3.3) *v* 76.5 (SD 4.6) years; NS).

Results—Dementia, vascular dementia, central brain atrophy on CT, disability in activities of daily living and instrumental activities of daily living, urinary incontinence, gait disorder (assistance needed), personality change, and night time confusion were found to be more commonly present in leuko-araiosis positive patients than in controls, whereas focal neurological symptoms and signs were not associated with leuko-araiosis. The occurrences of heart failure and systolic hypotension—but not hypertension—were higher in the leuko-araiosis positive group than in the controls. Leuko-araiosis was also found to be related to a less sudden onset of symptoms and a lower Hachinski score than true brain infarction(s).

Conclusions—Leuko-araiosis on CT in these elderly patients seems to be a vascular disorder aetiologically different from brain infarction, with clinical manifestations of subtle onset and general disabling nature and no prominent focal neurological signs or symptoms.

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Keywords: elderly; computed tomography; dementia; leuko-araiosis, vascular dementia

Neuropathological lesions involving cerebral white matter have long been observed as areas of hypodensity on CT in Binswanger's disease, leukodystrophies, multiple sclerosis, brain oedema, hypertensive encephalopathy, and several other diseases.¹ More recently, hypodense zones surrounding the frontal and occipital horns, unrelated to these conditions, have been seen regularly in elderly normal subjects and demented patients.¹⁻⁵ There are controversial opinions regarding the clinical relevance and aetiopathogenesis of these lesions. Hachinski and colleagues created the descriptive radiological label "leuko-araiosis" for these non-specific abnormalities to be replaced in the future with greater understanding as their true nature inevitably emerges.⁶

To elucidate the clinical characteristics and relevance of pure leuko-araiosis in a geriatric inpatient and outpatient population of Turku City Hospital, we decided to conduct a retrospective study on clinical manifestations of leuko-araiosis.

Patients and methods

PATIENTS

In the geriatric department of Turku City Hospital, CT examination of the brain was performed for various reasons in 252 patients from January to December 1989. It was standard practice in the department that the neurologist examined patients with neurological or mental problems and decided whether CT examination of the brain was necessary. The hospital records of these patients were interpreted by the same neurologist (ST-S) without knowing whether leuko-araiosis was present, but otherwise knowing the findings on CT. It was possible to obtain sufficient data on 206 patients. Of these, 112 were excluded because of brain infarction(s) ($n = 88$) or other disease ($n = 24$: eight intracerebral haematomas, two contusions, five hydrocephalia, two tumours, one contusion + haematoma, one contusion + hydrocephalus, one tumour + hydrocephalus, three subdural hematomas, and one multiple sclerosis) on CT except leuko-araiosis. Thereafter, groups with ($n = 26$) and without ($n = 26$) leuko-araiosis (with pure leuko-araiosis and with a normal CT finding respectively) were matched for age by excluding patients one by one from the upper and lower ends of the age range—that is, all the patients over 82 years of age in the group with leuko-araiosis ($n = 40$) and under 70 years of age in the group without leuko-araiosis ($n = 54$)—so that the mean ages of the two groups did not differ significantly (78.6 (SD 3.3) *v* 76.5 (SD 4.6) years; NS).

In addition, of the patients with infarction(s), an age matched group ($n = 26$) of patients with pure infarction(s) (no simultaneous leuko-araiosis or other pathology) was formed (mean ages: infarction(s) 75.6 (SD 5.7) *v* normal CT 76.5 (SD 4.6) years, NS).

Two patients were re-examined with CT of the brain in 1992, died in 1993-4, and underwent neuropathological examination. Patient 1 died at the age of 91 and patient 2 at the age of 85.

CLINICAL INFORMATION

The following data were collected from the hospital records: possible dementia,⁷ type and grading (mild, moderate, severe) of dementia,

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confusion, personality change, depression, emotional lability, somatic complaints, disability in activities of daily living or instrumental activities of daily living, gait disorder, urinary incontinence, focal neurological symptoms and signs (motor or sensory disorder attributable to a focal neurological lesion: abnormal power or tone in limbs, involuntary movements, abnormal deep tendon reflexes, extensor plantar response, primitive reflexes, cerebellar dysfunction, sensory abnormality, hemianopia, dysarthria, dysphasia, dyspraxia, right-left confusion, central cranial nerve dysfunction), dysphasia/arthritis, extrapyramidal disorder, reflexes, plantar sign, sudden onset, stepwise progression and fluctuating course of symptoms, occurrence of hemiparesis and a history of stroke, a diagnosis of clinical arteriosclerosis (symptomatic cardiovascular arteriosclerotic disease), arterial hypertension, diabetes, heart failure, coronary artery disease, and orthostatic hypotension, systolic and diastolic blood pressure, and the ischaemic score of Hachinski. The hospital routine included the measurement of blood pressure in a sitting position in the morning. All ECG recordings were interpreted according to the Minnesota code by the same internist who was unaware of the clinical history of the patient.⁸ In addition, results of routine EEG recordings were gathered from the hospital files. General and focal abnormality as well as mean occipital frequency were registered.

COMPUTED TOMOGRAPHY

All CT findings were interpreted by the same neuroradiologist (TK), who was unaware of the clinical data. A Toshiba 80A scanner was used in all examinations. The scans had been obtained from the base to the vertex of the brain. The slice thickness was 10 mm with the exception of the base of the brain where the slice thickness was 5 mm. The evaluation was done using hard copy x ray films.

Bilaterally symmetric confluent areas with reduced CT attenuation contiguous with the

margins of lateral ventricles were designated leuko-araiosis lesions. Areas with decreased attenuation of the white matter may be located at the margins of the frontal and occipital horns of the lateral ventricles or they may extend towards the centrum semiovale. Lesions may be irregular or patchy but mostly they tend to be uniform and diffuse.

The distribution of leuko-araiosis was divided into three areas: frontal, corpus, and occipital. The extent of leuko-araiosis in these areas was graded on visual impression as follows: 0 = no leuko-araiosis, 1 = under a quarter of the area, 2 = a quarter to a half of the area, and 3 = over half of the area. The intensity of the leuko-araiosis lesions was not taken into account because of the difficulty of comparing different images. A score for the severity of leuko-araiosis was constructed on the basis of the extent of the lesions from 0 to 9 (maximum 3 points in three areas). Lesions graded from 1 to 2 were considered mild, those from 3 to 5 moderate, and those over 5 severe.

Focal changes suggesting previous cerebral infarction were also registered. Central lacunae and porencephalic cysts, and localised atrophies with a distribution corresponding to major brain arteries were considered postinfarction lesions. To simplify matters, the different types of infarctions (for example, lacunae *v* larger cortical infarcts) were not differentiated even if they may have been consequences of different pathophysiological processes.

Central and cortical atrophy were evaluated visually and graded as follows: 0 = no atrophy, 1 = mild atrophy, 2 = moderate atrophy, 3 = severe atrophy. The size of the lateral ventricles was used as an estimate of central atrophy; the evaluation was done separately in anterior and posterior areas (maximum 3 points in the two areas = 6). The degree of cortical atrophy was graded by estimating the size of the cortical sulci in three areas: frontal, temporoparietal, and occipital (maximum 3 points in three areas = 9).

CLASSIFICATION OF DEMENTIA

The diagnosis and grading of dementia were based on DSM-III-R.⁷ On the basis of clinical data and findings on CT, the patients were divided into five groups: (a) no dementia; (b) Alzheimer's disease diagnosed in accordance with the NINCDS-ADRDA criteria for "probable Alzheimer's disease"; (c) Vascular dementia diagnosed in accordance with the NINDS-AIREN criteria¹⁰ for "probable vascular dementia" and ischaemic score of Hachinski¹¹; (d) combined dementia (predominantly like Alzheimer's disease with, however, features of vascular dementia—that is, focal neurological findings or Hachinski score ≥ 4); (e) other dementia (aetiology other than Alzheimer's disease or vascular dementia—for instance, alcoholism, previous trauma, or schizophrenia).

STATISTICAL ANALYSIS

The differences between means (age) were

Table 1 Sex, age, dementia diagnosis, and vascular factors in patients with and without leuko-araiosis (LA)

	LA absent (n=26) n (%)	LA present (n=26) n (%)	P value
Sex: Women	17 (65.4)	21 (80.8)	NS
Age: Mean (SD)	76.5 (4.6)	78.6 (3.3)	NS
Range	70.9–92.0	71.0–82.9	
Dementia	14 (53.8)	21 (80.8)	0.0385
pVaD+CD	6 (23.1)	14 (53.8)	0.0226
pAD	6 (23.1)	3 (11.5)	NS
History of paresis	9 (34.6)	10 (38.5)	NS
History of stroke	15 (57.7)	14 (53.8)	NS
Clinical arteriosclerosis	13 (50.0)	16 (61.5)	NS
Systolic hypotension < 130	3 (11.5)	9 (34.6)	0.0483
Orthostatic hypotension	1 (3.8)	5 (19.2)	NS
History of arterial hypertension	8 (30.8)	8 (30.8)	NS
Diabetes	5 (19.2)	5 (19.2)	NS
Heart failure	3 (11.5)	9 (34.6)	0.0483
Coronary artery disease	7 (25.9)	7 (26.9)	NS
Electrocardiography:			
Atrial fibrillation	2 (7.7)	3 (11.5)	NS
AMI*	8 (32.0)	7 (28.0)	NS
LVH*	2 (8.0)	4 (16.0)	NS

*Could not be interpreted in two patients (one in each group) because of left bundle branch block.

pVaD + CD = probable vascular dementia and combined dementia; pAD = probable Alzheimer's disease; AMI = myocardial infarction; LVH = left ventricular hypertrophy.

Table 2 Symptoms and signs and other clinical manifestations in patients with and without leuko-araiosis (LA)

	LA absent (n=26) n (%)	LA present (n=26) n (%)	P value
Disability	10 (38.5)	18 (69.2)	0.0261
Gait disorder, assistance needed	6 (23.1)	16 (61.5)	0.0050
Incontinence	7 (26.9)	15 (57.7)	0.0247
Mental change	3 (11.5)	11 (42.3)	0.0124
Confusion at night	6 (23.1)	13 (50.0)	0.0438
Hachinski score > 7	11 (42.3)	15 (57.7)	NS
Depression	4 (15.4)	5 (19.2)	NS
Emotional lability	5 (19.2)	9 (34.6)	NS
Somatic complaints	19 (73.1)	20 (76.9)	NS
Sudden onset of symptoms	8 (30.8)	11 (42.3)	NS
Stepwise deterioration	4 (15.4)	8 (30.8)	NS
Fluctuating course	11 (42.3)	15 (57.7)	NS
Focal neurological symptoms	14 (53.8)	10 (38.5)	NS
Focal neurological signs	12 (46.2)	13 (50.0)	NS
Extrapyramidal signs	6 (23.1)	8 (30.8)	NS
Brisk reflexes*	3 (15.0)	4 (20.0)	NS
Positive plantar sign*	6 (30.0)	9 (45.0)	NS
Dysphasia/-arthria	6 (23.1)	4 (15.4)	NS
Computed tomography (CT):			
Central atrophy	18 (69.2)	26 (100.0)	0.0021
Cortical atrophy	24 (92.3)	24 (92.3)	NS
Electroencephalography (EEG):			
General abnormality	12 (42.6)	13 (50.0)	NS
Focal abnormality†	7 (38.9)	6 (33.3)	NS
Mean occipital frequency < 8 Hz	16 (61.5)	19 (73.1)	NS

*Data were not available in 12 patients, six in each group.
†Data were not available in 16 patients, eight in each group.

compared by Student's *t* test. Comparisons between groups with and without leuko-araiosis were made using Pearson's χ^2 test. When the minimum expected value of the cell was < 5, Fisher's two tailed exact test was used. Comparison between the extent of pure leuko-araiosis on CT and age was made using Pearson's correlation coefficient. Comparisons between the extent of pure leuko-araiosis and the severity of dementia, cerebral atrophy, and other factors were made using the Kruskal-Wallis test. Differences were considered significant at $P < 0.05$.

Results

CLINICAL FEATURES

Of the original material of 182 patients (infarctions included, but other pathology except leuko-araiosis on CT excluded), leuko-araiosis on CT was found in 94 (51.6%) patients. Of these 40 had pure leuko-araiosis (leuko-araiosis as the sole lesion on CT with no other pathological findings). Both leuko-araiosis as a whole and pure leuko-araiosis were strongly associated with age ($P = 0.0000$) and, thus, the groups of patients with and without leuko-araiosis had to be age matched.

Of the 26 patients with (pure) leuko-araiosis, 10 had mild, 12 moderate, and four severe white matter lesions. Only nine of the 52 patients included in the study had Alzheimer's disease; three of them were leuko-araiosis positive and six were leuko-araiosis negative. One of the patients with Alzheimer's disease had leuko-araiosis only occipitally with 2 leuko-araiosis points, and the other two in all three areas (frontal, corpus, and occipital) with 3 and 5 points. Four of the five patients with vascular dementia were leuko-araiosis positive: one frontally with 1 leuko-araiosis point, two frontally and occipitally with 2 and 3 points, and one in all three areas with 7 points. Ten of the 15 patients with combined dementia had leuko-araiosis: three frontally and occipitally with 2 points each, and seven in all three areas with 3, 4, 5, 5, 7, 8, and 9 points. Of the five patients with other dementia, two had leuko-araiosis frontally with 1 point each and one in all three areas with 5 points. Of the 18 non-demented patients six had leuko-araiosis: two frontally with 1 leuko-araiosis point each, two frontally and occipitally with 3 and 5 leuko-

Neuropathological findings in patient 2. Amyloid positive material in the vessels located in the subarachnoid space: (A) positive staining with Congo red and (B) yellowish green birefringence with polarising light; bar = 100 μ m. (C and D) numerous vessels in the cortex positive for amyloid material (staining as in A and B); bar = 100 μ m.

araiosis points, and two in all three areas with 3 and 4 points.

Of the vascular factors studied (table 1), systolic hypotension < 130 and heart failure were found to be more common in patients with leuko-araiosis than in those without. On the other hand, clinical arteriosclerotic manifestations and risk factors for arteriosclerosis were not associated with leuko-araiosis. The severity (extent) of leuko-araiosis was, however, found to be associated with clinical arteriosclerosis ($P = 0.010$), atrial fibrillation ($P = 0.043$), and also vascular dementia ($P = 0.039$).

Table 2 shows the relation between the occurrence of leuko-araiosis and clinical manifestations. Dementia, vascular dementia, general disability, gait disorder, incontinence, mental change, and night time confusion were more common in patients with leuko-araiosis than in patients without, whereas focal neurological symptoms and signs and other clinical features studied were not associated with leuko-araiosis. The severity of leuko-araiosis was not, however, associated with the occurrence ($P = 0.84$, NS) or severity ($P = 0.56$, NS) of dementia. Central and cortical brain atrophy was almost constantly present in patients with leuko-araiosis; central atrophy was less common in leuko-araiosis negative patients. The presence ($P = 0.0021$) and severity ($P = 0.0000$) of central atrophy were associated with the presence of leuko-araiosis. The severity of central atrophy was not, however, found to be related to the severity of leuko-araiosis ($P = 0.225$, NS). An EEG was not found to differentiate between the patients with and without leuko-araiosis.

When we compared an age matched group of patients with pure infarctions with the group of patients who had a normal CT, infarctions were found to be associated with sudden onset of symptoms (80.8% *v* 30.8%, $P = 0.0003$), focal neurological symptoms (92.3% *v* 53.8%, $P = 0.0003$) and signs (92.3% *v* 46.2%, $P = 0.0000$), Hachinski score > 7 (92.3% *v* 42.3%, $P = 0.0000$), clinical arteriosclerosis (80.8% *v* 50.0%, $P = 0.0197$), arterial hypertension (46.2% *v* 19.2%, $P = 0.0385$), and diabetes (46.2% *v* 19.2%, $P = 0.038$).

NEUROPATHOLOGICAL CASE REPORTS

Patient 1

A woman had cardiac failure and atrial fibrillation and a tendency to orthostatic hypotension. Her cognition was normal in 1989, but in 1992 mild dementia was found. Brain CT showed progression of leuko-araiosis from moderate in 1989 to severe in 1992. Cerebral infarctions were not found, but mild central and moderate cortical atrophy was present. Pulmonary embolism caused her death in 1993 at the age of 91.

The neuropathological findings showed mild Alzheimer type changes combined with pronounced accumulation of amyloid in the walls of subarachnoidal and cortical vessels. Additionally, white matter showed alterations similar to those in Binswanger's disease.

At necropsy, the fresh brain weight was 1040 g. The external surface of the brain showed up to moderate atrophy of the gyri, mainly in the frontal and temporal lobes. In the transverse sections, white matter was grossly unremarkable and only mild cystic changes were noted in the lentiform nucleus. Histological examination showed a moderate number of neuritic plaques in the cortex and some neurofibrillary tangles with Bielschowsky staining. Congo red staining showed a pronounced accumulation of amyloid not only in the walls of subarachnoid vessels (figure, A, B) but also in the cortical vessels (figure, C, D). The vessels located in the white matter seemed to be Congo negative. The white matter showed diffuse, focal loss of myelin with luxol fast blue staining and the number of cells containing small, round, dark nuclei similar to those seen in oligodendrocytes were decreased in these areas. The number of axons was focally decreased and some fragmented as well as long, swollen axons were noted. These changes were similar to those termed grade II changes by Englund and Brun.¹² The walls of the vessels located in the white matter were thickened and contained fibrotic and hyalinous areas similar to those present in Binswanger's disease. The lentiform nucleus showed rather mild changes similar to *état criblé* and only occasional leuko-araiosis changes.

Patient 2

A woman had heart failure, latent diabetes, and orthostatic hypotension. She had moderate dementia in 1989, and moderate to severe dementia in 1992. Brain CT showed moderate leuko-araiosis in 1989 as well as in 1992, and mild central and cortical atrophy, but no infarctions. Pulmonary embolism caused her death in 1994 at the age of 85.

The neuropathological findings were in accordance with senile dementia of the Alzheimer type and, additionally, changes similar to congophilic angiopathy could be seen as well as diffuse changes in white matter similar to grade I changes according to Englund and Brun.¹²

At necropsy, frontal, temporal, and parietal lobes showed moderate atrophy of the gyri. The transverse sections disclosed multiple cystic changes similar to lacunar changes mainly in the lentiform nucleus but also in the cerebral white matter. The white matter around the cystic areas appeared greyish. Mild dilatation of brain ventricles was noted. The substantia nigra appeared slightly pale. Only mild arteriosclerotic changes in the cerebral arteries were seen. Bielschowsky silver staining showed loss of cortical neurons and the presence of numerous cortical plaques and neurofibrillary tangles. Numerous vessels containing amyloid positive material were seen in the subarachnoid space and some also in the cortex. However, the vessels in the white matter were negative to Congo red. The walls of the vessels located in the white matter were thickened and slightly homogeneous. Around the vessels, numerous cystic changes similar to lacunar changes and *état criblé* were noted. The white

matter showed diffuse loss of myelin with luxol fast blue staining and mild loss of axons. These changes were similar to those termed grade I changes by Englund and Brun.¹² Numerous astroglial cells were noted in the white matter. An increased periventricular gliosis was seen.

Discussion

In the present study, patients with leuko-araiosis as the sole finding on CT were more often demented than patients with normal CT. This is in accordance with the apparent fact that the incidence of leuko-araiosis on CT is higher in demented populations than in non-demented elderly subjects.^{2,3,13,14} The severity of leuko-araiosis was not, however, associated with the occurrence or severity of dementia. It has been suggested that cognitive function would not directly correlate with the severity of leuko-araiosis seen on CT or MRI but rather with the disturbed brain metabolism determined with PET.¹⁵ Furthermore, the severity of changes in white matter may not be related to the severity of neurological deficits; white matter changes may even be asymptomatic, and multiple lacunar infarcts or associated degenerative diseases (Alzheimer's disease) may be the main cause of dementia in patients with changes in white matter.¹⁶ In this study, patients with vascular dementia and especially combined dementia with predominant involvement of both frontal and occipital or all three areas of the brain, dominate and mostly influence the results. Conclusions as regards other groups of dementia and non-demented subjects and also other distributions of leuko-araiosis must be drawn with caution. The retrospective nature of the study has only a minor influence on the reliability of the results, because all the notes were documented by the same person and the reliability of hospital records in Finland is good.

The frequency of leuko-araiosis was also strongly associated with increasing age, in accord with most of the previous studies.^{1-5,13} Kobari and coworkers found an even stronger association between cerebral atrophy and leuko-araiosis.^{4,13} Increased ventricular size is, however, a very non-specific finding as it is the most common neuroradiological finding in both Alzheimer's and vascular dementias and it is also associated with normal aging.¹⁷

In the present study, all but one of the 26 patients with pure leuko-araiosis had frontal lucencies. This explains the association of leuko-araiosis with the neurological findings, including urinary incontinence, in the present study. Also Bennett and colleagues¹⁸ found urinary incontinence to be associated with lesions in the white matter, whereas others have found either a similar tendency² or no such relation.¹⁹ There have been some studies indicating an association of leuko-araiosis with gait impairment^{2,15,18} and a tendency to fall.²⁰ Studies that have found focal neurological symptoms and signs to be related to leuko-araiosis have been very small² or have also included patients with true brain infarctions

(Binswanger's disease).^{3,21} Mirsen and colleagues²² found no association between periventricular and subcortical or deep white matter lesions on MRI and focal neurological signs. The results of the present study agree with previous studies indicating an association of leuko-araiosis with gait impairment, but no association with focal neurological deficits was found. The finding of general disability associated with leuko-araiosis in this study accords with the most recent studies, in which leuko-araiosis has been found to be associated with admission to hospital,²³ with early institutionalisation, and with physical limitations,²⁴ with dependence of activities in daily living,²⁵ and with less focal and more generalised, confusional symptomatology^{26,27} of the cerebrovascular/ischaemic type.¹⁹ In vascular patients with pure leuko-araiosis a non-apoplectic type of disease development has been found.²⁸

Leuko-araiosis has been shown to be associated with various vascular factors.¹ Recently leuko-araiosis has been seen in hypotensive patients,^{19,29} which suggests general hypoperfusion as an aetiological factor, whereas hypertension seems to be associated with Binswanger's disease in most reports.³⁰ The present study supports these findings: leuko-araiosis was associated with systolic hypotension and heart failure, and infarctions were associated with hypertension and diabetes. It has been proposed that systemic haemodynamic disturbances induce hyalinosis (arteriosclerosis) on the walls of small cerebral vessels resulting in narrowing of the lumen and cerebral hypoperfusion, which, in turn, causes leuko-araiosis and also vascular dementia.^{31,32} Unfortunately, an orthostatic test was not performed routinely at the hospital. The severity (extent) of pure leuko-araiosis was associated with the presence of clinical arteriosclerosis, atrial fibrillation and also vascular dementia. This suggests that a thromboembolic mechanism of pathogenesis may also contribute to the genesis of severe cases of leuko-araiosis that approach, or perhaps lead to multi-infarcts or Binswanger's disease. In fact, the white matter changes have been proposed to be a continuum from mild to more severe changes, from different degrees of (selective) incomplete infarction to complete infarctions.¹² The role of amyloid angiopathy as one possible cause of leuko-araiosis is interesting.^{16,33} Amyloid deposits in cortical segments of long penetrating arterioles found in the two case reports of the present study could be partially responsible for hypoperfusion and hypoxaemia of the deep white matter.³⁴

In conclusion, the results suggest that pure leuko-araiosis on CT has a clinical manifestation of subtle onset and general disabling nature (dementia, vascular dementia, central brain atrophy on CT, disability in activities of daily living or instrumental activities of daily living, urinary incontinence, gait disorder (assistance needed), personality change and night time confusion) with no prominent focal signs or symptoms. It seems to be a vascular disorder different from true brain infarction both clinically and aetiologically.

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