Vascular deaths in elderly neurological patients with leukoaraiosis

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Abstract

***Objectives*—The prognostic significance of leukoaraiosis is still not completely elucidated. The objective was to examine survival and causes of death among elderly neurological patients with leukoaraiosis.**

***Methods*—From 1 January 1994, vital status and causes of death were drawn from municipality lists and death certificates of 216 patients (mean age (SD) 70·6 (8·3) years) admitted to a geriatric unit who underwent cranial CT between 1 January 1984 and 31 December 1986 (mean observation period (SD) 8·4 (0·8) years). These patients had been enrolled for a study of clinical predictors of leukoaraiosis. Based on the presence of leukoaraiosis on CT, this group had been divided into two subgroups of patients, with and without leukoaraiosis. The difference in survival and causes of death between these groups formed the objective of the study.**

***Results*—Survival time was shorter among the 90 patients with leukoaraiosis than among the 126 patients without (median survival time 4·07 *v* 7·78 years, log rank test $P < 0·001$). After controlling for age and other major death predictors, the risk of death remained significantly increased (relative risk (RR) = 1·64, 95% confidence interval (95% CI) 1·15–2·34) among patients with leukoaraiosis. Moreover, patients with leukoaraiosis had an almost threefold higher risk of dying from vascular causes than patients without (RR = 2·81, 95% CI 1·74–4·53).**

***Conclusion*—Leukoaraiosis is a predictor of vascular deaths in elderly neurological patients. Careful diagnostic evaluation and attention to preventive measures are required in patients with leukoaraiosis.**

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Leukoaraiosis is a term coined to describe radiological abnormalities seen on brain CT of elderly patients as bilateral areas of hypodensity in the white matter of the cerebral hemispheres.[1]

Although the pathogenesis is still incompletely defined, leukoaraiosis has been associated with various vascular risk factors and diseases, mainly hypertension, stroke, and heart disease.[2-4] A vascular pathogenesis of leukoaraiosis is also suggested by pathological findings: leukoaraiosis corresponds to areas of loss of myelin associated with alterations of the small parenchymal vessels,[5] in a region of the white matter regarded as a border zone.[6] Moreover, PET data[7] show that the reduction of cerebral blood flow in areas of leukoaraiosis is coupled with an increase in oxygen extraction rate, suggesting an ischaemic condition of the white matter.

Only recently has attention been drawn to the possible prognostic importance of leukoaraiosis. In patients with a history of cerebrovascular accidents[8 9] or probable Alzheimer's disease[10] it has been found that the presence of leukoaraiosis is associated with an increased risk of subsequent stroke. A study of our own showed that, in comparison with neurological controls without leukoaraiosis, patients with extensive leukoaraiosis and motor impairment carry an increased risk of stroke and myocardial infarction.[11] In this study leukoaraiosis had no effect on time to death, but controls without leukoaraiosis had been deliberately matched with cases for vascular risk factors.

In the present study we sought to examine whether the presence of leukoaraiosis predicts death or vascular death irrespective of clinical presentation or degree of leukoaraiosis. For this purpose we followed up until death a cohort of elderly neurological patients who had been examined between 1984 and 1986 for a study of clinical predictors of leukoaraiosis.[12] Possible differences in survival and causes of death (vascular and non-vascular) between patients with and without leukoaraiosis were the object of the present study. The availability from the original study of an extensive set of data on vascular risk factors, comorbid conditions, and clinical characteristics allowed us to verify whether the potential prognostic importance of leukoaraiosis regarding death was independent of other death predictors.

Patients and methods

Detailed information on methods and patients have been published elsewhere.[12]

PATIENTS AND END POINT DEFINITIONS

Study subjects were patients consecutively admitted for rehabilitation to the geriatric hospital "I Fraticini" (Florence, Italy) who underwent a cranial CT between 1 January 1984 and 31 December 1986. Activities of this hos-

Table 1 Demographic characteristics and diagnosis at discharge in the 216 patients

	Patients with LA (n = 90)	Patients without LA (n = 126)	Total (n = 216)
M/F	44/46	67/59	111/105
Mean age* (SD) (y)	73·7 (6·5)	68·3 (8·8)	70·6 (8·3)
Diagnosis:			
Cerebrovascular disease (%)	55·6	46·4	50·2
Non-vascular dementia (%)	22·2	31·2	27·4
Parkinson's disease (%)	5·6	11·2	8·8
Normal pressure hydrocephalus (%)	2·2	3·2	2·8
Other (%)	14·4	8·0	10·8

*At the time of CT.
LA = leukoaraiosis.

Table 2 Risk factors and leukoaraiosis

	Leukoaraiosis		
	Yes (n = 90)	No (n = 126)	OR (95% CI)
	%	%	
Sex: men	48·9	53·2	0·84 (0·49–1·45)
History of TIA	13·3	12·7	1·06 (0·47–2·36)
History of stroke	38·9	34·1	1·23 (0·70–2·15)
Hypertension	63·3	50	1·73 (0·99–3·00)
Diabetes	13·3	14·3	0·92 (0·42–2·03)
History of heart disease	17·8	18·3	0·97 (0·48–1·96)
Myocardial infarction	5·6	7·1	0·76 (0·25–2·36)
Cardiac arrhythmias	16·7	15·1	1·13 (0·54–2·36)
Left ventricular hypertrophy (ECG)	17·8	11·9	1·60 (0·75–3·43)
Dyslipidaemia	12·2	14·3	0·84 (0·37–1·87)
Proteinuria	34·4	31·7	1·13 (0·64–2·01)
Smoking	25·6	31·0	0·77 (0·42–1·40)
	Mean (SD)	Mean (SD)	P value
Systolic blood pressure (mm Hg)	148·0 (21·6)	146·9 (21·1)	0·697
Diastolic blood pressure (mm Hg)	84·3 (11·1)	86·2 (10·8)	0·211
Blood glucose (mg/dl)	92·9 (30·4)	88·7 (18·4)	0·203
Blood cholesterol (mg/dl)	220·5 (53·5)	229·0 (46·9)	0·170
Blood uric acid (mg/dl)	4·89 (1·29)	5·11 (1·52)	0·259
Blood creatinine (mg/dl)	1·24 (0·41)	1·27 (0·26)	0·600
Packed cell volume (%)	41·6 (4·7)	43·3 (3·9)	0·004
Urine density	1020·3 (3·3)	1019·3 (3·4)	0·035

TIA = Transient ischaemic attack.

Table 3 Neurological features and leukoaraiosis

	Leukoaraiosis		
	Yes (%) (n = 90)	No (%) (n = 126)	Odds ratio (95% CI)
Symptoms:			
Motor impairment	47·8	42·1	1·26 (0·73–2·17)
Gait disturbances	38·9	14·3	3·82 (1·98–7·35)*
Sphinter disturbances	15·6	5·6	3·13 (1·21–8·11)*
Vertigo, syncope, seizures	32·2	25·4	1·40 (0·77–2·54)
Dysphagia	7·8	6·3	1·24 (0·43–3·56)
Psychiatric disturbances	50·0	54·0	0·85 (0·50–1·47)
Signs:			
Psychiatric abnormalities	7·8	12·7	0·58 (0·23–1·47)
Dysphasia	14·4	17·5	0·80 (0·38–1·68)
Cranial nerve deficits	32·2	37·3	0·80 (0·45–1·41)
Facial deficit	26·7	32·5	0·75 (0·41–1·37)
Gait abnormalities	63·3	41·3	2·46 (1·41–4·29)*
Ataxic	17·8	8·7	2·26 (0·99–5·14)
Paraparesis	11·1	3·2	3·81 (1·16–12·60)*
Parkinson type	8·9	11·9	0·72 (0·29–1·78)
Hemiparetic	26·7	19·8	1·47 (0·77–2·79)
Involuntary movements	11·1	14·3	0·75 (0·33–1·71)
Spasticity	18·9	11·9	1·72 (0·81–3·66)
Increased tendon reflexes	61·1	45·2	1·90 (1·09–3·30)*
Extensor plantar response	34·4	17·5	2·48 (1·32–4·68)*
Cerebellar signs	14·4	6·3	2·49 (0·99–6·29)
Primitive reflexes	40·0	20·6	2·56 (1·40–4·69)*
Palmomental	24·4	8·7	3·28 (1·55–7·40)*
Sucking	26·7	13·5	2·33 (1·17–4·66)*
Glabellar tap	16·7	11·1	1·60 (0·73–3·51)
Dementia	46·7	44·4	1·09 (0·63–1·88)

*Odds ratios significantly different from unity.

Table 4 CT findings and leukoaraiosis

	Leukoaraiosis		
	Yes (%)	No (%)	Odds ratio (95% CI)
Lacunar infarct	24·4	3·2	9·87 (3·26–29·82)*
Non-lacunar infarct	10·0	31·7	0·24 (0·11–0·52)*
Normal pressure hydrocephalus	23·3	7·1	3·96 (1·72–9·12)*
Cerebral atrophy	58·9	31·7	3·08 (1·75–5·41)*

*Odds ratios significantly different from unity.

pital include neurorehabilitation and geriatric medicine (each accounting for about half of the admissions). Most patients with acute or chronic diseases of the CNS who were admitted to the hospital during the study period were examined with cranial CT. Out of the 291 patients on whom CT had been performed, 218 patients had CT images suitable for the study. These 218 patients formed the cohort who were evaluated clinically in the previous study[12] and who were considered in the present follow up study.

Information on vital status and primary causes of death was achieved by reviewing municipality death lists and death certificates looking for those patients who had died between 1 January 1984 and 31 December 1993. As of 1 January 1994 it was possible to obtain information on the vital status of 216 out of the 218 patients (mean observation period (SD) 8·4 (0·8) years). Based on the radiological assessment, 90 (41·7%) had leukoaraiosis and 126 (58·3%) did not. The two patients (0·9%) who were lost to follow up belonged to the group with no leukoaraiosis on CT. Table 1 reports the demographic characteristics and discharge diagnoses in the two groups. Tables 2–4 show risk factors, neurological characteristics, and CT data (with frequencies and mean values). Ninety eight of the 216 patients were demented. Types of dementia were distributed as follows: 54 (55·1%) with Alzheimer's disease, 36 (36·7%) with vascular dementia, and eight (8·2%) with other types. Leukoaraiosis was present in 31·5% of patients with Alzheimer's disease, 58·3% with vascular dementia, and 50% with other types of dementia.

From the January 1994 assessment, 131 (60·6%) of the 216 patients were dead and 85 (39·4%) were alive. Two independent referees (DI and MC), blind to the clinical and radiological characteristics of the patients, examined death certificate diagnoses to divide primary causes of death into vascular and non-vascular. Vascular death comprised death from stroke, myocardial infarction, and other vascular deaths. This leukoaraiosis group encompassed chronic cerebrovascular diseases (International Classification of Diseases, Revision 9 (ICD-9),[13] code 437), chronic cardiac diseases (codes 402, 414, 427, 429), and mixed vascular causes (codes 415, 438, 459). The agreement between the two observers in grouping causes of death, as assessed by κ statistics,[14 15] was very good (κ = 0·94). In the four patients in whom they were discordant agreement was ultimately reached by consensus between the two raters.

CT VARIABLES

All the scans were evaluated by the same observer (DI) who was blind to the clinical features and risk factor profile of the patients. As the evaluation was based only on visual observation, the definition of the main radiological variables was first validated by an agreement test between observers measured by κ statistics.[14 15] One neuroradiologist, one senior neurologist, and one junior neurologist,

blind to the clinical features of the patients, were asked to evaluate independently from each other the CT examinations of 30 patients for defining the CT variables leukoaraiosis, lacunar infarcts, non-lacunar infarcts, and cerebral atrophy. The criteria adopted and the agreement achieved in the definition of each variable were as follows: (1) leukoaraiosis: visual identification of patchy or diffuse symmetric areas of low attenuation (intermediate density between that of the normal white matter and that of intraventricular CSF) with ill defined margins limited to the periventricular white matter or extended to the centrum semiovale; the agreement on the assessment of this finding was substantial ($\kappa = 0{\cdot}67$); (2) lacunar infarcts: small (less than 2 cm in diameter), round or oval in shape, sharply demarcated hypodense areas in the deep cerebral matter; the agreement on this item was moderate ($\kappa = 0{\cdot}51$); (3) non-lacunar infarcts: this category comprised sharply demarcated, cortically extended, wedge shaped hypodense areas, with or without local enlargement of homolateral ventricles and sulci, subcortical hypodense areas larger than 2 cm in diameter, and watershed infarction; the agreement on this item was substantial ($\kappa = 0{\cdot}62$); (4) cerebral atrophy, rated into two categories: (*a*) no atrophy, including no atrophy, or atrophy limited to the basal or cortical sulci; (*b*) atrophy, when both cortical sulci and lateral ventricles were enlarged; κ for this variable was 0·55. Scans were also assessed for signs suggestive of normal pressure hydrocephalus as indicated by vassilouthis (prominent dilatation of the unobstructed ventricular system, "rounding" of frontal horns of lateral ventricles, and obliteration of the cerebral sulci).[16]

RISK FACTOR VARIABLES

Categorical variables were the following: (1) sex; (2) history of transient ischaemic attacks: focal neurological deficit of less than 24 hours in duration; (3) history of stroke: focal neurological deficit of more than 24 hours in duration; (4) hypertension: previous diagnosis of hypertension, or history of antihypertensive treatment, or blood pressure values higher than 160/95 mm Hg on at least two different measurements; (5) diabetes, defined according to the criteria of the National Diabetes Data Group,[17] including patients with impaired glucose tolerance; (6) history of heart disease, including history of angina, myocardial infarct, rhythm disturbances, valvopathies, or ECG signs of ischaemia or infarct, rhythm disturbances, and left ventricular hypertrophy; (7) myocardial infarction based on history; (8) cardiac arrhythmias based on history; (9) left ventricular hypertrophy on ECG; (10) dyslipidaemia: previous or current findings of abnormal cholesterol or triglyceride values; (11) previous or intercurrent smoking; (12) proteinuria.

Continuous variables were: (1) age; (2) systolic and diastolic blood pressure; (3) urine density; (4) packed cell volume; (5) fasting glucose; (6) total cholesterol; (7) triglycerides; (8) uric acid; (9) creatinine. Urine density, together with creatinine and proteinuria, were studied as indicators of arteriolar nephrosclerosis.

CLINICAL FEATURES

Table 3 shows the neurological symptoms and signs that were assessed. Dementia was defined according to the DSM-III criteria.[18] The mini mental state examination,[19] the Blessed dementia scale, and the Wechsler adult intelligence scale[21] were used as measures of cognitive functions. Functional status was assessed with the activities of daily living scale of Katz *et al.*[22] Information on social functioning was collected in a non-structured fashion by the nurses and social workers of the geriatric team.

STATISTICAL ANALYSIS

Because of the large age difference between the two groups of patients with and without leukoaraiosis, the effect of leukoaraiosis in predicting death had to be controlled for age. Besides age, there were other risk factors and comorbid conditions known to be associated with both age and leukoaraiosis that could influence the prediction of death among patients with leukoaraiosis. To verify whether leukoaraiosis had an independent effect on death we used Cox's regression analysis.[23] Among baseline variables as important predictors of death in our sample, we selected sex, previous stroke, hypertension, diabetes, heart disease, and dementia. For each of the three end points (all deaths, death from stroke, and death from vascular causes) leukoaraiosis was examined as a predictive variable together with age and the other covariate variables by means of three separate Cox regression models. The results were expressed as relative risk (RR) with 95% confidence intervals (95% CIs).[24]

Table 5 Causes of death in patients with and without leukoariosis

	Patients with LA (n = 90)	*Patients without LA (n = 126)*	*Total (n = 216)*
Total deaths	66 (73·3%)	65 (51·6%)	131 (60·6%)
Stroke (ICD codes 430–4)	16 (17·8%)	16 (12·7%)	32 (14·8%)
Myocardial infarction (ICD code 410)	2 (2·2%)	4 (3·2%)	6 (2·8%)
Other vascular deaths	31 (34·4%)	11 (8·7%)	42 (19·4%)
Chronic or less defined cerebrovascular diseases (ICD code 437)	18 (20·0%)	8 (6·3%)	26 (12·0%)
Chronic or less defined cardiac diseases (ICD codes 414, 402, 427, 429)	8 (8·9%)	3 (2·4%)	11 (5·1%)
Others (ICD codes 415, 438, 453, 459)	5 (5·5%)	0 (—)	5 (2·3%)
Non-vascular causes	15 (16·7%)	34 (27%)	49 (22·7%)
Unknown	2 (2·2%)	—	2 (0·9%)

LA = leukoariosis.

Table 6 Prediction of death from any cause, vascular, and stoke death (Cox proportional hazard models) by leukoaraiosis and other potential predictors of death

	RR (95% CIs)		
Variables	*Total death*	*Vascular death*	*Stoke death*
Leukoaraiosis	1·68 (1·18–2·39)*	2·85 (1·76–4·59)*	1·89 (0·88–4·07)
Age†	1·36 (1·19–1·55)*	1·41 (1·18–1·69)*	1·34 (1·03–1·75)*
Male sex	1·46 (1·02–2·10)*	1·77 (1·10–2·83)*	1·89 (0·89–4·04)
Previous stroke	1·63 (1·08–2·47)*	1·76 (1·04–2·99)*	2·31 (0·98–5·43)
Hypertension	1·54 (1·08–2·21)*	1·96 (1·24–3·11)*	1·87 (0·90–3·88)
Diabetes	1·08 (0·63–1·83)	1·67 (0·91–3·04)	3·10 (1·38–6·97)*
Heart disease	2·07 (1·32–3·26)*	2·58 (1·46–4·56)*	3·02 (1·33–6·88)*
Dementia	2·42 (1·66–3·54)*	2·54 (1·56–4·14)*	1·23 (0·56–2·69)

*Odds ratio significantly different from unity.
†Risk per five year age group.

When analysing each specific cause of death, patients who died from other causes were considered as censored data. Moreover, we sought to determine whether among all the baseline variables (risk factors and clinical or radiological features) we had available in our database, there were other possible confounders or modifiers. We used a forward stepwise method to examine leukoaraiosis together with this larger set of variables in relation to death and specific causes of death grouped as indicated above.

Results

The proportion of deceased patients in each group was 66/90 in the leukoaraiosis group and 65/126 in the non-leukoaraiosis group. The median survival time was shorter among patients with than among those without leukoaraiosis (4·07 years *v* 7·78 years; log-rank test $P < 0·001$).

Table 5 shows the deaths and causes of death in the total cohort and in the two groups of patients—with and without leukoaraiosis. In two of the 131 patients who died it was not possible to define the cause of death because death certificates were missing. Both these patients showed leukoaraiosis on CT. The number and percentages of patients who died from any cause, from stroke, or from other vascular causes were all higher among the leukoaraiosis than the non-leukoaraiosis group (table 5). Among patients who died from vascular causes, 32 died from stroke, six from myocardial infarction, and 42 from other vascular causes. The last group included mainly deaths from chronic cerebrovascular or cardiac diseases. Deaths from myocardial infarction occurred infrequently, with no substantial difference, in either group.

After controlling for age and other major predictors of death, patients with leukoaraiosis had a 1·5-fold higher death risk, and an almost threefold (RR = 2·80, 95% CI 1·74–4·53) higher risk of dying from a vascular cause than patients without leukoaraiosis (table 6). Both these risk increases were significant. The risk of dying from stroke was also increased among patients with leukoaraiosis but the difference was not significant. Table 6 gives information on significance of the other major predictors of death.

To examine the weight of chronic cerebrovascular diseases (ICD-9 code 437; a condition in which leukoaraiosis is supposedly frequent) in predicting vascular death, we carried out the same analysis excluding the patients deceased from this cause (treated as censored data in the Cox model). The relative risk of vascular death remained substantially unchanged (RR = 2·62, 95% CI 1·45–4·72).

For the analyses carried out with leukoaraiosis and the larger set of baseline variables, leukoaraiosis again turned out to be a significant independent predictor of death from any cause (RR = 1·45, 95% CI 1·01–2·09). Other independent predictors were age, myocardial infarction, motor disturbances, cognitive impairment, blood creatinine, and CT showing normal pressure hydrocephalus. Considering stroke death, leukoaraiosis showed a positive but not significant predictive effect (RR = 1·27, 95% CI 0·62–2·57); the significant predictors were age, motor disturbances, and creatinine values. For vascular death, leukoaraiosis had a significant predictive effect (RR = 2·78, 95% CI 1·72–4·50), together with age, cardiac disease, motor disturbances, cognitive impairment, and creatinine values.

Discussion

Our results indicate that leukoaraiosis predicts vascular death in elderly neurological patients. This seems independent of age and other risk factors and comorbid conditions (including previous stroke) known to be associated with leukoaraiosis. The association with death from stroke alone is less striking.

By contrast with previous outcome studies,[8 9 11] we examined a less specific group of patients with leukoaraiosis. In fact, our study sample consisted of patients with various neurological diseases, although half of them had cerebrovascular disease. Moreover, we included patients with any degree of leukoaraiosis. This might explain some differences from previous studies[8 11] which had shown an increased risk of stroke or death from stroke.

The cause of death in patients with leukoaraiosis was the object of a recently published study that had been carried out in Finland.[25] Similarly to ours, this study examined patients admitted to a geriatric department. Different from our study, it was retrospective, and did not consider the possible confounding effect of risk factors. However, the conclusion that leukoaraiosis was more strictly associated with death from cardiovascular causes than death from stroke is consistent with our finding.

The results of our study have to be regarded with some caution. The causes of death were based on death certificate diagnoses. The reliability of this type of diagnosis is questioned. Studies of validity of diagnoses from death certificates have been conducted in Italy within the "Seven Countries Study": sensitivity and specificity values were over 70% and 90% for the diagnoses of death from myocardial infarction and from stroke respectively.[26] The diagnoses of chronic or less defined cardiovascular diseases are presumably less reliable. However, in our study, possible inaccuracies

in death diagnoses should have affected the two groups of patients equally.

The conclusion drawn from our findings may be limited by a few factors. The study population was a subsample of all the neurological patients admitted to our geriatric hospital during the study period. In the preceding paper on these patients,[12] we discussed the selection bias related to the exclusion of some patients because CT had not been performed or had yielded poor quality images. After examining the characteristics of these patients, we found that they were not different from the included patients according to demographic data and risk factors. Most of the excluded patients were those who were uncooperative in the CT examination, and therefore were presumably more severely demented than the included ones. We have no further way to judge whether and in which way this selection could have affected our conclusions. Although in that period "I Fraticini" Hospital admitted the vast majority of elderly neurological patients requiring rehabilitation in our area, we cannot be sure that these patients were representative of all elderly neurological patients occurring in the population.

Despite these shortcomings, we think that our study is of value for the following reasons:

(1) data on the prognostic importance of leukoaraiosis were scanty; (2) the patients were studied prospectively; (3) we had a group of patients without leukoaraiosis as controls; (4) we had a large set of baseline information on risk factors and comorbid conditions to be studied as covariates in relation to the prediction of death.

Our results suggest that leukoaraiosis can be regarded as a marker of cardiovascular disease. This is in agreement with other clinicopathological and laboratory findings indicating an ischaemic origin of these radiological appearances in patients with multiple vascular risk factors and several associated cardiovascular abnormalities.[5 7] Consequently, elderly patients presenting with neurological problems and leukoaraiosis on CT should be investigated for cardiovascular abnormalities and given appropriate treatment.

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