ORIGINAL ARTICLE

Leukoaraiosis and pulse-wave encephalopathy: Observations with phase-contrast MRI in mild cognitive impairment

Leucoaraïose et encéphalopathie liée à l’onde de pouls : une étude par IRM de flux dans les déficits cognitifs légers

M.-C. Henry-Feugeas a,*, C. Roy b, G. Baron b, E. Schouman-Claeys a

a Department of Radiology, Bichat–Claude-Bernard University Hospital, AP–HP, 46, rue Henri-Huchard, 75877 Paris cedex 18, France
b Department of Epidemiology, Biostatistics and Clinical Research, Bichat–Claude-Bernard University Hospital, AP–HP, 46, rue Henri-Huchard, 75877 Paris cedex 18, France

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KEYWORDS
Leukoaraiosis;
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MRI;
Mild cognitive impairment

Summary
Purpose. — To test the pathogenic hypothesis of a breakdown in the vital buffering of the arterial pulsations behind leukoaraiosis (LA) in mild cognitive impairment (MCI).
Methods. — Seventy-one elderly patients with MCI underwent a combined structural and dynamic MR examination (3D T1-weighted and fast-FLAIR T2-weighted sequences, phase contrast sequences). Arterial indices of pulsatility (IP) and composite indicators of the amplitude transfer function between cerebrospinal fluid and cerebral venous flow (I_{csf/veins}) were used to assess the large artery stiffness and the intracranial compliance respectively. Cerebral total arterial blood flow (tCBF), superficial and deep venous flow rates were also measured. Intracranial dynamic parameters and potential confounders including age, gender and vascular risk factors were compared between two groups respectively with and without significant LA.
Results. — The only dynamic changes on multivariate analyse were an IP increase, a lowering of deep venous outflow and I_{csf/veins} in patients with LA. There was a significant interaction between IP and I_{csf/veins} in the logistic regression: as compared with patients with low IP (suggestive of high large artery compliance) and high I_{csf/veins} (suggestive of high intracranial compliance), the adjusted odds ratios for the presence of LA were 9 (95% CI 1–64, P = 0.02) in cases of both high IP and high I_{csf/veins}, 10 (95% CI 1–64, P = 0.02) in cases of both high IP and low I_{csf/veins} and 19 (95% CI 3–127, P = 0.002) in cases of both low IP and low I_{csf/veins}.
Conclusion. — LA may reflect an arteriosclerotic and/or resistive pulse wave encephalopathy in MCI.

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* Corresponding author.
E-mail address: marie-cecile.henry-feugeas@bch.aphp.fr (M.-C. Henry-Feugeas).

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Introduction

The prevalence of bilateral and either patchy or diffuse white matter changes on neuroimaging sharply increases with ageing: this "silent epidemic" of so-called leukoaraiosis (LA) is likely to affect one third of apparently healthy subjects aged 65 and older and is still more frequent in demented elderly [1]. This age-related vascular white matter degeneration [2] is a fundamental part of the pathology associated with late life dementia [3–5], a major global health problem with rapid demographic ageing. Understanding LA pathophysiology is thus a major challenge, particularly in a population at high risk of dementia such as the elderly with mild cognitive impairment (MCI). However, despite several decades of study, current attempts of therapeutic research are still hampered by persistent controversies on the basic pathomechanisms of LA.

Age-related white matter changes are traditionally believed to result from an insidious reduction in cerebral arterial inflow. However, this ill-defined concept of "incomplete infarct" is challenged by a growing body of observations; these changes are located around, rather than at the end of the abnormal arterial segment, which suggests "edema-related gliosis" rather than infarcts [6,7], there is no significant lumen obstruction in cerebral small vessel diseases underlying LA [8] and the relationship between LA and cerebral blood flow rates is unclear [9]. Alternatively, disturbances in the vital buffering function required to smooth pulsatile outflow from the heart—or so-called windkessel dysfunction—may be implicated in LA pathogenesis [6,10,11]; there is increasing evidence of an association between LA and various biomarkers of reduced arterial compliance [12–16], whereas surgical improvement of craniospinal compliance may reverse LA [17]. However, to our knowledge, the potential roles and respective contributions of disturbances in vascular and craniospinal compliance to LA pathogenesis have not yet been investigated in the elderly with MCI.

Besides providing detailed morphological analysis of white matter changes [6], phase-contrast magnetic resonance imaging (MRI) now allows non invasive and reliable assessment of both vascular and cerebrospinal fluid CSF flow waveforms [18–22]. Thus, the aim of this study was to test the hypothesis of disturbances in large artery and/or intracranial compliance behind LA in MCI using this dynamic MR analysis.

Materials and methods

Population

The 71 study subjects (mean age: 72 ± 5 years) were all patients enrolled in a longitudinal MR research program on the early diagnosis of Alzheimer’s disease, the MRI of cognitive decline (MRI CODE) study [21]. All of them gave written informed consent and the study was approved by the local medical ethics committee. Briefly, they were otherwise apparently healthy elderly subjects with MCI, but no major abnormalities on preliminary clinical and biological examination.

MRI protocol

Scans were acquired on a 1.5 T imager (Signa; General Electric Medical System, Milwaukee, WI) as previously described [21]. Briefly, the structural examination included a T2-weighted fast sequence with the FLAIR technique and a 3D T1-weighted coronal fast SPGR sequence. Phase-contrast cine sequences (TR 20–23 ms; TE 7.6–9.9 ms; 2 NEX; flip angle 30°; matrix 256 × 256; 2 NEX; 5 mm thickness; flow compensation) were used for flow quantification. With retrospective cardiac gating using peripheral pulse, 16 quantitative flow-encoded images covering the whole cardiac cycle were obtained per plane of slice; through the aqueduct, through the distal basilar artery, the vertical portion of the internal carotid arteries, the straight sinus and the superior longitudinal sinus (Fig. 1) [21].

Image analysis and processing

Grading of white matter changes was made by a single operator using a previously described reproducible 3D analysis [6,21,22]. Both fast FLAIR T2-weighted and 3D T1-weighted sequences were reviewed to determine the presence or absence of subependymal caps larger than 5 mm around the frontal horns, of marked splenial changes, of significant subcortical white matter changes [6,21,22]. This last class included deep white matter changes larger than 10 mm, subcortical grey matter changes larger than 5 mm, bands along the long white matter tracts, and the so-called "traumatic" LA (marked splenial changes, larger subependymal changes). Presence of subinsular subcortical changes was also considered as indicator of significant LA.

All MR measurements were made using a commercial flow analysis package (CV flow; General Electric Medical System, Milwaukee, WI). Regions of interest (ROI) were manually drawn outlining the aqueduct and vascular structures on the phase images (Fig. 1). Background ROI were placed in the adjacent brain stem to correct arterial and CSF flow velocities, in the adjacent occipital parenchyma to correct venous flow velocities (Fig. 1).

For each of the 16 time frames, the product of the mean velocity and the corresponding ROI area provided an estimate of the volume flow rate through the studied structures [21]. These measurements allowed the determination of the following vascular conduct parameters: total cerebral blood flow (tCBF) as the sum of volume flow rates from the internal carotid arteries and the basilar artery, superficial and deep venous outflow respectively through the superior sagittal sinus and the straight sinus.

Parameters of windkessel function included indicators of large artery and craniospinal compliance.

The arterial pulsatility index (IP) was used to assess large artery windkessel function [21].

The amplitude transfer functions XFR_{CSF/ST} and XFR_{CSF/SS} were also calculated to describe the sinusoidal response of respectively the straight venous sinus and the superior sagittal venous sinus to a sinusoidal driving force, CSF pulse wave. The CSF and venous flow waveforms per cardiac cycle were fitted as a periodic function, with a period equal to the length of the cardiac cycle and then broken into sine wave components or harmonics using discrete Fourier anal-
Figure 1  Flow MR measurements. ROI measurements used in the MR analysis of intracranial dynamics were drawn on velocity encoded MR images of the vessels and aqueductal CSF flow; around the basilar trunk (A, long arrow), the internal carotid arteries (A, short arrows), the straight sinus (B, long arrow), the superior sagittal sinus (B, short arrow) and the aqueduct (C, arrow). Background ROI were systematically performed (A, B and C, arrowheads).

ysis. XFR\textsubscript{CSF/ST} and XFR\textsubscript{CSF/SS} were calculated by taking the ratio of the amplitude of the corresponding harmonics of the output signal and input signal:

\[
\text{Amplitude XFR} = \frac{\text{harmonic amplitude (output signal)}}{\text{harmonic amplitude (input signal)}}
\]

In the studied population with various heart rates, only the amplitude transfer functions of the fundamental frequency were considered [18] and a composite index of CSF venous transmission \(I_{\text{CSF/veins}}\) was calculated by the product of the fundamental frequency of the amplitude transfer functions XFR\textsubscript{CSF/ST} and XFR\textsubscript{CSF/SS}.

This composite indicator of the amplitude transfer function between cerebrospinal fluid and cerebral venous flow was used to assess the craniospinal windkessel function or compliance; it decreases with reduced overall intracranial compliance and subsequent higher ventricular CSF pulse wave and lower venous pulse wave, that is, lower coupling of CSF and veins pulsations [14,18].

All measurements were made by the same operator. High values of the intraclass coefficients of correlation of tCBF (0.919), deep and superficial venous outflow rates (respectively 0.879 and 0.907), as well as of arterial pulsatility indices (0.986) and \(I_{\text{CSF/veins}}\) (0.995) were obtained in a randomly selected subgroup of 20 subjects and confirmed good reproducibility of the phase contrast measurements.

Statistical analysis

The MR measurements were compared between patients with at least one form of significant LA (or LA+ patients) and the remaining patients without any form of significant LA (or LA− patients). These MR parameters included the tCBF, deep and superficial venous outflow rates, IP and composite \(I_{\text{CSF/veins}}\) indices.

Potential bias related to age, gender, heart rates, vascular risk scores — as assessed with a composite cardiovascular disease risk score integrating presence of arterial hypertension, diabetes, dyslipidemia and smoking [21] were also systematically researched.

The preliminary analysis used Mann Whitney or Fisher’s exact according to the nature of the variables. To find outcomes related to the presence of significant LA, a multiple logistic regression analysis was then performed. This analysis included variables demonstrating a \(P\) value $\leq 0.2$ on univariate analysis. Variables retained in the multivariate model were selected by a stepwise procedure.

To evaluate the respective role of large artery and craniospinal windkessel functions, the interaction between local \(I_{\text{CSF/veins}}\) and arterial (IP) windkessel functions was tested by entering interactions terms (IP and \(I_{\text{CSF/veins}}\)) in this logistic regression. For this evaluation, we used two classes of IP values to allow for a non linear relation, low and high IP respectively equal/above the median value of 1.08 of the whole study group and below this median value. \(I_{\text{CSF/veins}}\) values were also classified in two classes defining worse and better local windkessel functions; patients with composite \(I_{\text{CSF/veins}}\) indices within the lower 50th percentile, suggestive of low transmission of CSF pulsations to the veins, formed the group with lower intracranial compliance; the remaining patients defined the group with higher intracranial compliance.

Data were analyzed by using Statistical Analysis System release 9.1 statistical software package and a \(P < 0.05\) was considered as significant.

Results

On univariate analysis, patients with significant LA were older than those without any significant LA (74 ± 5 versus 69 ± 5 years, \(P = 0.0005\)), they had lower deep venous flow...
rates (110 ± 23 versus 129 ± 27 ml/mn, P = 0.005) and slightly lower total arterial cerebral flow rates (734 ± 131 versus 791 ± 110 ml/mn, P = 0.03). This LA+ group was also characterized by a higher frequency of the MR patterns of lower intracranial compliance (62% versus 31%, P = 0.01) and higher IP (64% versus 31%, P = 0.006, Fig. 1). Conversely, the LA+ and LA− groups of patients did not show any significant difference (P > 0.05) in terms of gender (24 women and 18 men versus 10 men and 19 women), cardiovascular disease risk scores (1.38 ± 1.10 versus 1.14 ± 1.06), heart rates (66 ± 9 versus 66 ± 11) or superficial venous outflow rates (278 ± 60 versus 291 ± 62 ml/mn).

Unlike lowering of total arterial cerebral flow rate, advancing age and lowering of deep venous flow rate remained independent predictors of LA in the multiple logistic regression (Table 1). There was also a significant interaction between arterial index of pulsatility and index of CSF venous coupling in the logistic regression so that three different dynamic patterns predicted LA; the MR pattern of high IP with high CSF veins coupling, the MR pattern of an isolated reduction in CSF veins coupling, the strongest predictor of LA in this study group, and finally the mixed pattern of both high pulsatility index and low CSF veins coupling (Table 1, Figs. 1—4).

**Table 1** Outcomes related to LA and interaction between arterial index of pulsatility and index of cerebrospinal fluid (CSF) venous coupling in the logistic regression.

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio (IC 95%)</th>
<th>P</th>
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<tbody>
<tr>
<td>Age</td>
<td>1.16 (1.01—1.34)</td>
<td>0.04</td>
</tr>
<tr>
<td>Deep venous flow rate</td>
<td>0.97 (0.94—0.99)</td>
<td>0.02</td>
</tr>
<tr>
<td>Higher CSF venous coupling</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low IP</td>
<td>1 (reference)</td>
<td></td>
</tr>
<tr>
<td>High IP</td>
<td>9.41 (1.37—64)</td>
<td>0.02</td>
</tr>
<tr>
<td>Lower CSF venous coupling</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low IP</td>
<td>19 (2—126)</td>
<td>0.002</td>
</tr>
<tr>
<td>High IP</td>
<td>10 (1.5—65)</td>
<td>0.02</td>
</tr>
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**Discussion**

In this study, LA was associated with a reduction in cerebral deep venous outflow but no significant change of cerebral...
increased PI with LA. Conversely, the observed association of increased PI, is not likely to contribute to the observed cerebral distal arteriolar lumen, another traditional cause of increased PI such as elevated intracranial pressure or decreased cardiac output are not likely to contribute to cerebral arterial inflow and LA in MCI patients with LA. The lack of significant association between cerebral arterial inflow and LA in MCI patients appeared in line with previous reports on LA and arterial flow rates in non MCI populations [9—14]. There was however a reduction in deep venous outflow in MCI patients with LA, whereas lower bilateral perfusion in the basal ganglia, thalamus, and frontal lobes has been related to LA in patients with dementia of the Alzheimer type (DAT) [23]. Indeed, vascular conduct function most often appeared preserved in MCI patients with LA. Our data also converge with the growing body of evidence that large artery stiffening is a factor of LA [15].

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This particular perfusion pattern in LA supports the pulse wave encephalopathy theory rather than that of ischemia. Indeed, it may result from the high vulnerability of deep perforating arterioles to insufficient dampening of the arterial pulsations, as these small vessels directly arise from the circle of Willis. Moreover, the increased transmission of the arterial pulse wave to the central brain — and especially the corpus callosum — in patients with reduced arterial and/or craniospinal compliance may alter early deep venous outflow through the vein of Galien, a strategic part of the deep venous system located in the near vicinity of the “mobile” posterior corpus callosum [10—14].

Our data also converge with the growing body of evidence that large artery stiffening is a factor of LA. The increased PI in elderly MCI patients with LA confirmed and extended previous reports of an association between increased PI and LA in elderly subjects from the general population [12], in neurological patients from a stroke center [13] and in middle-aged asymptomatic hypertensive patients [15].

These data also confirm the clinical value of the IP as a biomarker of large artery stiffening [21]. Indeed, other causes of increased PI such as elevated intracranial pressure or decreased cardiac output are not likely to contribute to elevation of the intracranial PI in our otherwise healthy elderly patients with MCI [13]. Previous studies of cerebrovascular changes in LA [8] also suggest that a reduction in cerebral distal arteriolar lumen, another traditional cause of increased PI, is not likely to contribute to the observed increased PI with LA. Conversely, the observed association between increased PI and LA appears in line with neuropathological evidence of a role of atherosclerosis and arteriosclerosis in white matter changes observed in aging and AD [24], as well as with the recently shown association between aortic stiffness and LA [16]. Indeed, reduced large artery compliance hampers dampening of the arterial pulsations and increases transmission of flow pulsations downstream into vasodilated organs, principally brain and kidney, damaging frail microvessels [6,10,11,25]. Growing evidence of a major overlap between Alzheimer’s disease and cerebrovascular disease in late-onset DAT now helps to understand the increased likelihood of progression to DAT in MCI patients with LA [3,5,21].

Such a role of arterial windkessel function in LA pathogenesis also fits well with the association between deep white matter changes and remote vascular changes such as large arteries stiffness or less frequently predominantly cortical and meningeal small artery changes. Indeed, small artery diseases implicated in LA all share a common feature of altered smooth muscle elements of the small vessels [26]; these alterations may impair compliance characteristics and ability to withstand distending pressure in this section of the vasculature [27].

In addition, our study indicates a striking association between LA and an MR indicator of intracranial compliance, suggesting that reduced intracranial compliance may be an alternative main determinant of LA in otherwise healthy patients with MCI.

Indeed, low coupling between CSF aqueductal pulse wave and cerebral venous wave suggests decreased subarachnoid CSF and/or venous “mobile” compliances [18]. In normal conditions, intracranial compliance allows for rapid regulation of intracranial pressure throughout the rapid systolic increase of intracranial arterial volume; rapid systolic increase of intracranial arterial volume into the rigid cranial cavity is compensated for by immediate CSF venting from the subarachnoid cranial spaces to the more compliant subarachnoid spinal spaces on one hand and rapid venous outflow from the cranial cavity on the other hand [28]. A reduction in any of these CSF and venous mobile compliances increases transmission of the arterial pulse wave to the aqueductal CSF but decreases transmission of CSF pulse wave to the collapsible subarachnoid veins; it leads to a lower coupling between CSF aqueductal pulse wave and cerebral venous wave [18].

Therefore, our data confirm a link between disturbances in CSF dynamics and LA pathogenesis [14,17,29];
Leukoaraiosis and pulse-wave encephalopathy

References


