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Original Research Article

Cerebrovascular Biomarker Profile Is Related to White Matter Disease and Ventricular Dilation in a LADIS Substudy

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Key Words

Biomarkers · Cerebrospinal fluid · Matrix metalloproteinases · Myelin basic protein · Neurofilament · Ventricular dilation · White matter disease

Abstract

Background: Small vessel disease (SVD) represents a common often progressive condition in elderly people contributing to cognitive disability. The relationship between cerebrospinal fluid (CSF) biomarkers and imaging correlates of SVD was investigated, and the findings were hypothesized to be associated with a neuropsychological profile of SVD. ***Methods:*** CSF SVD-related biomarkers [neurofilament light (NF-L), myelin basic protein (MBP), soluble amyloid precursor protein-β (sAPPβ), matrix metalloproteinases (MMPs), and tissue inhibitor of metalloproteinase (TIMP)] were analysed in 46 non-demented elderly with imaging findings of SVD. We assessed the relationship between the CSF biomarkers and white matter hyperintensity (WMH) volume, diffusion-weighted imaging and atrophy as well as their association with neuropsychological profiles. ***Results:*** The WMH volume correlated with ventricular dilation, which was associated with executive function and speed and attention. Increased WMH and ventricular dilation were related to increased CSF levels of TIMP-1, NF-L and MBP and to decreased sAPPβ. A positive correlation was found between the CSF biomarker MMP-9 and WMH progression. ***Conclusions:*** The link between progressive WMH and MMP-9 suggests an involvement of the enzyme in white matter degeneration. CSF TIMP-1, NF-L, MBP and sAPPβ may function as biological markers of white matter damage.

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Introduction

White matter disease caused by arteriolosclerotic lesions of the small penetrating arteries of the brain, in this context denominated 'small vessel disease' (SVD), represents a common and often progressive condition in elderly people. It has been found to give rise to various degrees of cognitive impairment and, in its pronounced form, it is known as subcortical ischemic vascular dementia (SIVD) [1]. The neuropsychological profile associated with SIVD differs from that of Alzheimer's disease (AD) with deficits in the executive functions and speed and attention domains [2]. The biochemical marker deviations and the refined magnetic resonance imaging (MRI) changes for these specific cognitive alterations are less well defined.

White matter hyperintensities (WMHs) visualized by MRI have, to a modest degree, been correlated with cognitive dysfunction [3]. Also, it is possible to have WMH without any sign of dysfunction, which might be explained by the type of damaged tissue and the extent of damage [4]. It is not fully understood how severe a demyelinating process must be before the neuronal function is compromised or cognitive dysfunction evolves. One way to address these questions is through the combination of biomarkers and neuropsychological evaluation. Imaging tools that allow for the assessment of white matter structural integrity, such as diffusion-weighted imaging (DWI), seem to be promising. The mean diffusivity, or the apparent diffusion coefficient (ADC), of tissue water depends on the structural integrity at a cellular and subcellular level [5]. Therefore, an increase in tissue water diffusivity is associated with a loss of tissue or cellular architecture for instance affected by a pathological process such as SVD. To compare the structural changes seen by conventional MRI, such as WMH volumetric and atrophic changes, with DWI of WMH and normal-appearing brain tissue (NABT) of the white and the gray matter and biomarkers could provide for a deeper molecular understanding. Cerebrospinal fluid (CSF) biomarkers reflecting SVD disease processes such as blood brain barrier disruption [matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs)] and white matter lesions [MMPs, neurofilament light (NF-L), myelin basic protein (MBP), and soluble amyloid precursor protein (sAPP)] might mirror early alterations in tissue damage, and thus, might be useful as markers in CSF. The neuropathological findings of amyloid plaques and neurofibrillary tangles found in the gray matter in pure AD and in patients with mixed cerebrovascular disease/AD (MIX) are associated with established AD biomarkers [total tau (T-tau), amyloid-β_{1-42} ($A\beta_{1-42}$) and phosphorylated tau (P-tau_{181})] [6–8] and might be used interchangeably with NABT ADC measurements for early disease detection. The baseline levels of the above CSF biomarkers were hypothesized to be associated with changes in the white and the gray matter, respectively, as assessed by MRI. Dysfunctions in speed and attention and executive functions were hypothesized to be associated with both the SVD biomarker profile and MRI changes of the white matter.

Material and Methods

Participants

This single-centre substudy of the LADIS (Leukoaraiosis and Disability in the Elderly) project included 46 individuals (22 women and 24 men; age 74 ± 5 years) (table 1) and is a continuation of a previous substudy of the LADIS project [9]. LADIS is a European longitudinal multi-centre study with the aim to investigate white matter lesion as an independent predictor of the transition to disability [10]. The inclusion criteria were: (a) age between 65 and 84 years; (b) hyperintensities of cerebral subcortical white matter on MRI, from mild to severe,

Table 1. Demography of patient material at baseline and at follow-up

	Baseline (n = 46)	Follow-up (n = 34)
Age, years	74±5	73±5
Female/male	22/24	15/19
MMSE	28.4±1.9	28.9±1.3
WMH volume, mm^3	24±18	22±17
Ventricular dilation	4.3±1.8	4.1±1.8
Sulcal atrophy	4.41±1.4	4.4±1.5
NABT ADC	1,329±122	1,312±136
NABT rPH[a]	0.01±0.001	0.01±0.001
Fazekas score	2.0±0.8	2.0±0.8

Data are means ± standard deviations. MMSE = Mini-Mental State Examination.

[a] The relative peak height reflects the number of voxels in normal-appearing white matter in relation to the total number of voxels contributing to the histogram.

according to the categorization of the Fazekas scale [11]; (c) no or mild disability as assessed by the Instrumental Activities of Daily Living scale [12], and (d) presence of a contactable informant. Exclusion criteria were: (a) subjects prone to dropout because of severe illnesses (cardiac, hepatic or renal failure, neoplastic or other relevant systemic disease); (b) severe unrelated neurological diseases; (c) leukoencephalopathies of non-vascular origin (immunologic-demyelinating, metabolic, infectious) revealed by brain imaging; (e) severe psychiatric disorders; (f) inability to give informed consent, and (g) inability or refusal to undergo cranial MRI scanning. All subjects underwent clinical examination including anamnesis and functional tests, such as global functioning, cognitive, motor, psychiatric, and quality-of-life measures. The study was approved by the Ethics Committee at the University of Gothenburg and was conducted in accordance with the Helsinki Declaration. All subjects gave their informed consent to participate in the study.

Neuropsychological Assessment

The neuropsychological test battery consisted of parts of the LADIS battery [13] with tests of speed and attention, episodic memory and executive functions. Speed and attention was assessed by the Trail Making Test A and B [14], the Symbol Digit Modalities Test and digit cancellation, whereas episodic memory was assessed by the word recall subtest from the Vascular Dementia Assessment Scale cognitive subscale [13] since the California Verbal Learning Test (CVLT) [15], which was used at the 3-year follow-up appointment, was not available at baseline. Executive functions were evaluated by the Stroop Colour Word Test (Victoria version) [16], verbal fluency (animal names generated in 1 min), a maze task, the backward digit span task [17] and subtraction scores from the Trail Making Test (B time – A time). Each test score was z-transformed in order to construct composite scores for each domain expressing the general level of performance within that domain. The sum of the z-scores of learning trials 1–5, delayed recall and recognition on CVLT were used for the episodic memory composite z-score. The z-scores of neuropsychological tests, where a higher score represented poorer performance, were inverted (–z) for the calculation of composite scores.

Biochemical Analyses

At baseline, patients were subjected to lumbar puncture through the L3/L4 interspace in the morning to avoid diurnal fluctuations in biomarker levels. CSF was collected in polypro-

pylene tubes and submitted to centrifugation at 2,000 *g* at room temperature for 10 min. The supernatant was aliquoted into screw-cap polypropylene tubes and stored at –80°C pending biochemical analyses. The CSF levels of T-tau, P-tau$_{181}$ and A$\beta_{1–42}$ were assessed by Luminex® xMAP® technology (INNO-BIA AlzBio3; Innogenetics, Gent, Belgium) [18]. NF-L was analysed by ELISA (NF-light®; UmanDiagnostics, Umeå, Sweden) [19] as was MBP (Active® MBP; Diagnostic Systems Laboratories Inc., Webster, Tex., USA). The MMPs (MMP-1, MMP-2, MMP-3, MMP-9 and MMP-10) were assessed by multiplex (MSD® Multi-Spot®) and TIMP-1 by singleplex electrochemiluminescent ELISAs (MSD Multi-Array®; Meso Scale Discovery, Gaithersburg, Md., USA). Intra-assay coefficients of variation were <10% for all assays, except for the MMP assays which were <15%.

Magnetic Resonance Imaging

MRI assessments were performed at the Sahlgrenska University Hospital, Gothenburg, Sweden, according to a standardized protocol (LADIS) in which a 1.5-tesla scanner was used to assess T1-weighted 3-dimensional magnetization-prepared rapid-acquisition gradient echo (coronal and sagittal plane), T2-weighted fast-spin echo (axial plane) and fluid-attenuated inversion recovery (FLAIR; axial plane) sequences. All scans were collected centrally, and the WMH ratings were performed on FLAIR images. The Fazekas [11] and Scheltens [20] scales were used for visual staging of the WMH, and quantitative assessments were done with a semiautomated volumetric technique [21] performed on the same sequences, including the infratentorial region. The progression of WMH was evaluated at follow-up with the extended Rotterdam Progression Scale [22]. Lacunes were identified by number through a combination of FLAIR, MP-RAGE (magnetization-prepared rapid-gradient echo) and T2 images [23].

DWI was performed on the 1.5-tesla whole-body system with a pulsed-gradient spin-echo sequence with an echo planar imaging readout with 2 b factors (b = 0 s/mm^2 and b = 900–1,000 s/mm^2). The diffusion gradients were applied along the three principal directions, and the voxel size was 1.95 × 1.95 × 1.95 mm. The DWI metrics included the average ADC, or mean diffusivity, of both WMH and NABT of the white and the gray matter. The relative peak height (rPH) and peak position (PP) of NABT were determined by histogram analysis. Further details are found elsewhere [24].

Ventricular dilation and sulcal atrophy were evaluated at the Department of Neurology at the Medical University of Graz by one rater. A rating scale previously assessed in other studies [25, 26] ranging from 1 (no atrophy) to 8 (severe atrophy) was employed. All MRI measurements evaluated in this study were baseline values except for the progression of WMH.

Statistical Analysis

The demographic, clinical and CSF data are presented as mean values and standard deviations. Univariate pairwise comparison was assessed by the Mann-Whitney U test for continuous variables between groups, and the non-parametric χ^2 test was used for dichotomous variables. Correlation analyses between MRI alterations and biomarker levels were performed using Spearman's rank correlation; the values are presented by Spearman's rank correlation coefficient (ρ). Associations between continuous baseline MRI variables and neuropsychological profiles assessed both at baseline and at 3-year follow-up were evaluated by linear regression. The patients displayed a large variability in cognitive impairment at baseline; thus, analyses of change over time, i.e. Δ (follow-up – baseline data), were not performed. All statistical analyses were performed with PASW statistics 18 (SPSS Inc., Chicago, Ill., USA).

Table 2. Correlation between baseline CSF biomarker levels and baseline MRI variables

	WMH volume	Scheltens total	WMH ADC	NABT ADC	NABT PP	Sulcal atrophy	Ventricle dilation	Rdam ext.
P-tau								
ρ				0.366	0.317	0.290		
Sig.	n.s.	n.s.	n.s.	0.015	0.036	0.045	n.s.	n.s.
n				44	44	46		
MMP-10								
ρ				0.432	0.306			
Sig.	n.s.	n.s.	n.s.	0.003	0.043	n.s.	n.s.	n.s.
n				44	44			
MMP-3								
ρ						0.348		
Sig.	n.s.	n.s.	n.s.	n.s.	n.s.	0.018	n.s.	n.s.
n						46		
MMP-1								
ρ				0.326				
Sig.	n.s.	n.s.	n.s.	0.035	n.s.	n.s.	n.s.	n.s.
n				44				
TIMP-1								
ρ	0.428	0.525	0.437				0.405	
Sig.	0.004	<0.001	0.002	n.s.	n.s.	n.s.	0.005	n.s.
n	43	45	46				46	
NF-L								
ρ	0.368	0.568	0.467		0.375		0.305	
Sig.	0.016	<0.001	0.001	n.s.	0.014	n.s.	0.039	n.s.
n	42	44	46		42		46	
MBP								
ρ		0.323	0.296		0.358			
Sig.	n.s.	0.032	0.048	n.s.	0.021	n.s.	n.s.	n.s.
n		44	45		41			
sAPPβ								
ρ	–0.332	–0.342					–0.451	
Sig.	0.027	0.023	n.s.	n.s.	n.s.	n.s.	0.002	n.s.
n	42	44					45	
MMP-9								
ρ								0.362
Sig.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	0.028
n								37

Rdam ext. = Rotterdam extended; Sig. = significance; n.s. = not significant.

Results

CSF measurements were performed on 46 patients of whom 44 underwent DWI assessments. Correlation analyses were performed between baseline biomarker levels and baseline MRI assessments to evaluate the biomarker relationship with specific tissue damage. The WMH volume, Scheltens total and ventricular dilation correlated with TIMP-1, NF-L and sAPPβ, while TIMP-1, NF-L and MBP correlated with WMH ADC (table 2). Ventricular dilation in turn correlated with WMH ADC (ρ = 0.363; p = 0.018), WMH volume (ρ = 0.466; p = 0.001) and Scheltens total (ρ = 0.337; p = 0.022). Furthermore, P-tau and MMP-10 correlated with NABT ADC and PP, while P-tau and MMP-3 correlated with sulcal atrophy (table 2). Moreover, NABT ADC, NABT rPH and NABT PP all highly correlated with sulcal atrophy (ρ = 0.699, p <

Table 3. Association between ventricular dilation and NABT alterations at baseline and neuropsychological functions at baseline and follow-up

	Baseline (n = 46)				Follow-up (n = 34)			
	Ventricular dilation	NABT rPH[1]	NABT ADC[2]	NABT PP[3]	Ventricular dilation	NABT rPH	NABT ADC	NABT PP
Memory function								
β	–0.36							
SE	0.12							
p	0.013	0.261	0.483	0.684	0.070	0.463	0.546	0.933
Speed and attention								
β	–0.35	0.48	–0.35	–0.39	–0.39			
SE	0.13	0.13	0.14	0.14	0.18			
p	0.019	0.001	0.024	0.010	0.023	0.051	0.111	0.085
Executive function								
β	–0.32	0.49	–0.33		–0.45			
SE	0.10	0.09	0.10		0.11			
p	0.031	0.001	0.033	0.109	0.008	0.114	0.121	0.527

The β value and SE are only shown for significant measures.

[1] rPH: lower values indicate less tissue with normal diffusivity in the analysed tissue compartment.

[2] ADC: higher values indicate higher diffusivity in the analysed tissue compartment.

[3] PP: a shift towards higher values indicates a global increase in diffusivity in the analysed tissue compartment.

0.001; ρ = –0.422, p = 0.005; ρ = 0.570, p < 0.001, respectively). The NABT metrics and sulcal atrophy did not correlate with any of the WMH measurements or ventricular dilation. The only CSF biomarker correlating with the progression of white matter changes was MMP-9 (table 2). The albumin ratio correlated with the concentration of TIMP-1 (ρ = 0.327; p = 0.028), but no correlation was found between the albumin ratio and any of the imaging variables.

Ventricular dilation, NABT ADC, NABT rPH and NABT PP were the only MRI variables found to be associated with the neuropsychological profiles. The relationship between these changes and CSF biomarkers was further investigated.

The continuous baseline MRI variables were assessed against continuous composite z-scores of the cognitive domains of memory, speed and attention and executive function in order to investigate which modalities were related (table 3). Increased ventricular dilation was associated with worse memory performance in the total material at baseline (n = 46), but also with worse speed and attention and poorer executive function together with increased NABT ADC and decreased NABT rPH. Furthermore, increased NABT PP was associated with a decrease in speed and attention. The CSF markers $A\beta_{1-42}$, P-tau and MMP-10 were the only fluid biomarkers (including albumin ratio) that were associated with cognitive profiles, i.e. memory function (p = 0.007, p = 0.041 and p = 0.040, respectively) and speed and attention (p = 0.001, p = 0.014 and p = 0.051, respectively), at baseline.

A subpopulation of patients (n = 34) was assessed to verify if the same baseline biomarker changes were important for the cognitive profile at follow-up. The subpopulation was based on the availability of CSF, MRI and neuropsychological baseline and follow-up variables and did not significantly differ from the total patient population (table 1). However, when assessing the baseline neuropsychological functions of the 12 patients who were excluded due to missing neuropsychological evaluation at follow-up, memory function was significantly worse (p = 0.021) compared to the 34 patients in the subpopulation. The other functions did

not significantly differ between the groups. Ventricular dilation at baseline was associated with speed and attention and executive function at follow-up. Both $A\beta_{1-42}$ and MMP-10 were associated with memory function ($p = 0.012$ and $p = 0.040$, respectively), while only $A\beta_{1-42}$ was associated with speed and attention ($p = 0.027$) at follow-up. There was also a trend towards an association between TIMP-1 and albumin ratio when looking at speed and attention ($p = 0.070$ and $p = 0.073$, respectively).

Discussion

The main finding was that WMH and ventricular dilation were related to altered baseline CSF levels of TIMP-1, NF-L, MBP and sAPPβ, which have previously been reported to be changed in patients with SIVD and MIX [9, 27, 28]. In addition, an association between baseline WMH volume and ventricular dilation, which in turn was associated with both baseline and follow-up executive function and speed and attention, was found.

At baseline, ventricular dilation was associated with worse performance in all cognitive domains. However, WMH was only indirectly related to cognitive functions through the correlation with ventricular dilation and changes in CSF sAPPβ, NF-L and TIMP-1 levels. It has previously been shown in several LADIS studies that the WMH volume is directly associated with poor longitudinal cognitive function [29], particularly with deterioration in psychomotor speed and executive functions [30]; it is likely that the disconnection in this substudy is due to the small sample size. Nevertheless, the WMH volume might be more subtle and ventricular dilation might capture early cell and tissue alterations that ultimately affect cognitive functions, and thus, might be an earlier marker of cognitive decline. The biomarkers seem to capture the WMH volume as well as total loss of brain tissue, which would reflect the overall function of the MMP/TIMP system and white matter-specific alterations such as axonal destruction reflected by NF-L, MBP and sAPPβ. The reduction in sAPPβ could also be due to decreased shedding regulated by the MMP system. Furthermore, the correlation between ventricular dilation and WMH volume and their relationship to the CSF biomarkers TIMP-1, sAPPβ and NF-L imply the importance of these changes to SVD and disability since it has previously been shown that MIX and SIVD patients share a changed CSF profile of the biomarkers TIMP-1, MBP, NF-L and $A\beta_{1-42}$ [27, 31].

Deterioration in executive functions and speed and attention is found in patients with SVD, which in this study population could relate to both SIVD and MIX. Therefore, it was intriguing to find a relationship between executive function and speed and attention at baseline and NABT metrics, since NABT ADC was also associated with the CSF markers $P\text{-tau}_{181}$ and MMP-10. Both these CSF markers are found at increased levels in MIX patients [27, 32]. Furthermore, there was a direct association between $A\beta_{1-42}$, P-tau and MMP-10 and cognitive dysfunction (memory function, speed and attention) at baseline, while $A\beta_{1-42}$ (memory function, speed and attention) and MMP-10 (memory function) were associated with cognitive functions at follow-up. Alterations in P-tau, $A\beta_{1-42}$ and MMP-10 levels are found in patients who primarily suffer from memory deficits, i.e. AD as well as MIX [27, 32], while $A\beta_{1-42}$ and MMP-10 are also altered in SIVD patients [27] with deficits in executive functions and speed and attention [2]. Speed and attention and executive functions remained significantly associated with ventricular dilation at follow-up, while neither NABT nor P-tau was associated with any functional domain. The patients who dropped out after baseline assessments performed significantly worse only on memory tasks compared to the population that was assessed at follow-up. Thus, the loss of association for P-tau at follow-up might be due to the drop in patients suffering mainly from memory deficits with known neuropathological findings of neurofibrillary tangles in the hippocampus and the entorhinal cortex

[33]. Furthermore, NABT metrics may be more often attributed to the disintegration of gray matter neurons and neuritis than to the white matter, which could explain the loss of association with cognitive dysfunction when patients with more severe gray matter alterations dropped out. This would also in turn explain why there were no associations between NABT measures and CSF biomarkers that have previously been shown to be altered in patients with pure SIVD (TIMP-1, NF-L, MBP and sAPP) [27].

In addition, MMP-9 was the only biochemical marker that was connected to progressive white matter lesions, and it has previously been shown to be elevated in MIX and SIVD patients as well as after stroke [27, 34]. The fact that MMP-9 has been related to the development of intracerebral haemorrhage [35] and been shown to be continuously elevated in patients with stroke progression and larger infarct volumes in the subacute phase [36] is possibly supporting a detrimental role of MMP-9. The potential role of MMP-9 as an early progression marker in CSF for white matter lesions, but also as a (SIVD) disease prognostic marker, needs to be further evaluated.

All CSF and MRI biomarkers were analysed at baseline in patients with no or only mild cognitive impairment, and the fact that the SIVD CSF markers seem to reflect biological changes in the white matter, as detected by MRI, at this early stage makes them even more interesting in terms of possible early diagnostic tools. However, studies with larger samples are warranted to elucidate the relationship between the structural and biomarker changes and to confirm the findings. The disconnection between the neuropsychological profiles and alterations in single CSF biomarkers will have to be further assessed. It is likely that a combination of CSF biomarkers might better reflect deficits in different cognitive domains and this is why some of the imaging variables seem to be more often related to cognitive deterioration than CSF variables. It is also possible that specific combinations of CSF biomarkers or more sensitive imaging tools, such as diffusion tensor imaging, could improve the recognition of more specific cognitive functions. All in all, the alterations in cognitive domains related to SIVD together with changes in CSF biomarkers reflecting the biological processes of the disease seem to be offering unique, but related, information that could contribute to an early diagnosis. It will also be important to determine the predictive value and the specificity of ventricular dilation for the development of cognitive dysfunctions that relate to AD and SIVD.

In conclusion, the intricate relationship between alterations in the biomarker levels of NF-L, MBP, MMP-9, TIMP-1 and sAPPβ and imaging changes in both WMH and ventricular dilation together with domain-specific alterations in neuropsychological functions point to a combined usefulness of these modalities as early diagnostic markers to reflect SVD pathological processes.

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Disclosure Statement

The authors report no conflicts of interest.

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