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Disproportionate ventricular dilatation in the elderly could be a manifestation of small vessel disease

Submitted

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Abstract

Ventricular dilatation out of proportion to the sulcal cerebrospinal fluid (CSF) volume is a characteristic of normal pressure hydrocephalus (NPH), but has also been described in the general population. We hypothesized that disproportionate ventricular dilatation could be caused by atrophy of the white matter based on small vessel disease. Our aim was to investigate the relationship between white matter hyperintensity (WMH) volume and disproportionate ventricular dilatation.

Data are based on 858 persons (35.4 % men, age range 66-92 years) who participated in the Age, Gene/Environment Susceptibility Study - Reykjavik Study. MRI was followed by segmentation of ventricular, sulcal and WMH volume. Disproportionate ventricular dilatation was measured using the ratio of ventricular volume and sulcal CSF volume, VV/SV. Linear regressions were used to study the relationship between WMH volume, ventricular volume, sulcal CSF volume, and VV/SV, adjusted by age, sex, smoking, hypertension, cardiac disease, blood cholesterol, diabetes, body mass index and total intracranial volume.

WMH volume was positively correlated with ventricular volume and VV/SV (both at $p < 0.001$). However, WMH volume showed a negative correlation with sulcal CSF volume ($p < 0.001$).

Our findings suggest that dilatation of the ventricles in patients with white matter hyperintensities may not be a mere reflection of small vessel disease based atrophy, but that it could be, at least partly, based on active expansion of the ventricles. This unexpected finding offers a new perspective on the pathophysiology of NPH.

Introduction

Disproportionate ventricular dilatation is the radiological hallmark of normal pressure hydrocephalus (NPH), a syndrome characterized by a relative increase in ventricular volume and impairment of gait, cognition and sometimes bladder function.[1-3] In a population-based study, it was demonstrated that this radiological phenomenon is often observed in the elderly and that it is associated with subclinical impairment.[4]

The cause of disproportionate ventricular dilatation is not known. However, patients with WMH often present with an enlarged ventricular system, as well as symptoms and signs similar to those seen in NPH.[5-7] Furthermore, there is firm evidence that WMH in the elderly are based on cerebral small vessel disease (SVD).[8] Based on these observations, we hypothesized that disproportionate ventricular dilatation is the consequence of selective central atrophy secondary to SVD. Since WMH are one of the main manifestations of SVD, we predicted that WMH would be associated with disproportionate ventricular dilatation.

Materials and methods

Patients

Subjects are participants in the Age, Gene/Environment Susceptibility (AGES) Reykjavik Study; a population study initiated to examine the contribution of genetic susceptibility and gene/environment interaction to phenotypes common in old age. The AGES is an extension of the Reykjavik Study (1967-1994); a prospective study of cardiovascular disease based on a cohort of men and women born 1907-1935 and living in Reykjavik at the time of baseline measure in 1967. All participants in the AGES Study underwent extensive evaluation, including MRI of the brain, neuropsychological testing, physical performance, a standard clinical evaluation, and an in-person questionnaire. This report is based on those participants examined from September 2002 until March 2004 (n = 2,300). The AGES Study was approved by the Icelandic National Bioethics Committee (VSN 00-063), the Icelandic Data Protection Authority, and by the institutional review board of the US National Institutes of Health.[9] All participants gave written informed consent.

MR image acquisition and post-processing

The MRI acquisition protocol and post-processing has been described in an earlier study.[4] The analyses required dual spin-echo (proton attenuation and T2-weighted) and Fluid-Attenuated Inversion Recovery (FLAIR) images, which were acquired at a field

strength of 1.5T (GE Medical Systems, Milwaukee, Wisconsin). The dual spin-echo scans were performed with a field of view of 220 mm, a 256 x 256 matrix size, section thickness of 3.0 mm, 54 slices and no slice gap. The FLAIR scans were performed with a field of view of 220 mm, a 256 x 256 matrix size, section thickness of 3.0 mm, 46 slices and no slice gap. All images were checked for cerebral infarcts by an experienced neuroradiologist. WMH segmentation was performed using a validated automatic image analysis pipeline. The algorithm consisted of a multi-spectral tissue classification, that has been described in detail in a previous publication.[10] Areas with increased signal on proton attenuation, T2-weighted and FLAIR images were identified as WMH.

To segment CSF volumes, we used previously described semi-automated segmentation software (SNIPER, Software for Neuro-Image Processing in Experimental Research) that combines knowledge-based fuzzy clustering and region-growing techniques.[11] Brain extraction was followed by an automated segmentation procedure that assigned CSF volumes within the skull. CSF belonging to the lateral and third ventricles was manually labeled as ventricular volume. The fourth ventricle was not included in our analysis. The volumetric assessment was repeated for 43 out of 834 subjects (5%) to analyze the intra-rater reliability in our sample. The assessment yielded an intra-class correlation coefficient greater than 0.99, indicating high intra-rater reliability. The program estimated total intracranial volume and total CSF (tCSF) volume. Sulcal CSF volume (SV) was calculated by extracting ventricular CSF volume (VV) from tCSF volume. Ventricular dilatation was expressed as VV/SV. These volumetric measures have been applied in a previous publication.[4]

Covariates

Based on previous studies, we adjusted for possibly confounding demographic (age and sex) and health history factors. Systolic and diastolic blood pressures, measured in supine position, were defined as the first and fifth Korotkoff sounds respectively. History of hypertension was defined as the use of antihypertensive medication or a systolic blood pressure equal to or higher than 140 mm Hg or a diastolic blood pressure equal to or higher than 90 mm Hg. History of coronary heart disease, diabetes mellitus and peripheral arterial disease were assessed with a combination of questionnaire and clinical data, including medication use. Smoking status (current or previous smoker versus non-smoker) and body mass index calculated from measured weight and height were also included as covariates.

Analytical sample

Of the first 2300 participants, 1988 had MRI scans (312 were only examined at home or had contraindications for MRI). Of these 1988, a total of 433 participants were excluded

due to an incomplete MRI scan, an MRI scan of suboptimal image quality precluding successful image post-processing, or automated image post-processing failures. Finally, to avoid a possible overestimation of sulcal CSF volume in the automated segmentation procedure that assigned CSF volumes within the skull, we excluded 697 subjects with significant cerebral or cerebellar infarcts, defined as parenchymal defects with a long axis diameter ≥ 4mm outside the basal ganglia, the midbrain or the cortex along the path of the medullary arteries, and with a short axis diameter ≥ 4mm within these areas. This resulted in a sample of 858 subjects with complete MRI post-processed data. Compared to those with complete MRI post-processing data, the group of excluded subjects was older and contained a higher percentage of males and subjects with depressive symptomology, coronary heart disease and diabetes mellitus (all significantly different at $p < 0.05$, adjusted for age and sex).

Statistical analysis

A linear regression analysis was used to study the relationship between WMH volume and ventricular dilatation, adjusted for age, sex, smoking, hypertension, coronary heart disease, diabetes and body mass index (IBM SPSS Statistics, version 20; IBM Corp., Armonk, N.Y.). In addition, linear regression analyses were used to study the relationship between WMH volume and ventricular or sulcal CSF volume, adjusted for total intracranial volume, as well as adjusted for age, sex, smoking, hypertension, coronary heart disease, diabetes and body mass index.

Results

Our study population of 858 persons ranged in age from 66 to 92 years of age, and had a wide variety of cardiovascular risk factors (Table 7.1). Volumetric assessment yielded a mean total intracranial volume of 1738.5 ml, a mean VV of 43.1 ml, a mean sulcal CSF volume of 279.6 ml, and a median WMH volume of 12.3 ml.

The associations between WMH volume, intracranial CSF compartments and disproportionate ventricular dilation are summarized in Table 7.2. WMH volume showed a significant positive association with VV, as well as with VV/SV, independent of demographic and cardiovascular risk factors and intracranial volume (both associations at $p < 0.001$, standardized coefficient beta 0.14 and 0.22 respectively). These findings indicate that increasing WMH was associated with both increasing ventricular volume and increasing disproportionate ventricular dilatation. WMH volume showed a significant negative association with SV, independent of demographic and cardiovascular risk factors and intracranial volume ($p < 0.001$, standardized coefficient

beta – 0.12). These findings indicate that increasing WMH was associated with decreasing sulcal CSF volume. In our adjusted model, none of the individual cardiovascular risk factors showed an independent association with VV/SV.

Table 7.1 Participant characteristics

	n = 858
Age, mean (SD)	75.0 (5.4)
Women (%)	64.6
Current or previous smoker (%)	60.0
Body mass index (SD)	26.9 (4.4)
Coronary heart disease (%)	18.8
Hypertension (%)	67.0
Diabetes mellitus (%)	7.7
Total intracranial volume, mean (ml)	1738.5
Ventricular volume, mean (ml)	43.1
Sulcal CSF volume, mean (ml)	279.6
WMH volume, median (ml)	12.3

Table 7.2 Association between WMH volume, intracranial CSF compartments and disproportionate ventricular dilation

	Beta (95% CI)
Ventricular volume	0.20 (5.09 – 9.48)
Sulcal CSF volume	-0.12 (-16.1 – -7.1)
Ventricular volume / sulcal CSF volume	0.28 (0.03 – 0.04)

After adjusting for age, sex, smoking, body mass index, blood cholesterol, coronary heart disease, hypertension, diabetes mellitus and intracranial volume, WMH volume shows a positive association with ventricular volume and disproportionate ventricular dilation, but a negative association with sulcal CSF volume.

Discussion

We observed that WMH volume has a positive association with both ventricular volume and disproportionate ventricular dilation, but a negative association with sulcal CSF volume. In the present study none of the cardiovascular risk factors (smoking, hypertension, body mass index, coronary heart disease and diabetes mellitus) showed an independent association with VV/SV, or disproportionate ventricular dilatation.

The association between WMH and ventricular dilatation has been extensively studied. A meta-analysis of 48 studies found a significant relation in the majority of studies, but did not find sufficient evidence to indicate that this relation is independent of shared risk factors, including vascular risk factors and age.[12] Subcortical arteriosclerotic encephalopathy (SAE) - a form of small vessel vascular dementia caused by damage to the white matter[13] - and NPH share a number of characteristics. Ventricular dilatation and an increased WMH load have been described in SAE,[5-7] as well as in NPH.[14,15]Arterial hypertension is found in the majority of patients with SAE,[16] and SAE has been associated with stroke and diabetes.[17] While we did not find an independent association of cardiovascular risk factors with disproportionate ventricular dilatation in the present study, others observed an association between a clinical diagnosis of NPH and arterial hypertension, cardiac disease, peripheral vascular disease, and ischemia in the deep white matter.[18-20] Furthermore, autopsy studies revealed that the vast majority of WMH in older persons are based on small vessel disease (SVD).[21] We hypothesized that widening of the ventricles in the elderly is caused by selective SVD-induced atrophy of the periventricular white matter. The correlation between WMH load and ventricular dilatation that we observed was in line with our hypothesis.

However, in addition to the association between increasing WMH and increasing ventricular volume, we also observed an association between increased WMH load and decreased sulcal CSF volume. This finding was unexpected, since in the case of mere parenchymal loss, the cortical sulci would be expected to widen as well, or, in case the atrophy would be selectively periventricular, stay the same. The increased volume of the ventricles and decreased volume of the sulcal CSF space that we found to be associated with WMH load suggests that the observed ventricular volume increase results from an outward displacement of the brain by expanding ventricles rather than from mere atrophy. This observation sheds new light on the pathophysiology of NPH.

NPH is associated with increased cerebral capillary pulsations,[22] and this association could provide an explanation for the relation we observed between expansion of the ventricles and WMH load. The origin of increased capillary pulsations in NPH may be the consequence of systemic arterial disease. Mitchell *et al.* demonstrated that increased stiffening of the aorta, assessed by pulse wave velocity measurements, gives rise to increased propagation of pulsatile energy into the vascular bed of end organs such as kidneys and brain.[23] In addition, they demonstrated that in the elderly increased aortic stiffness, resulting in a similar stiffness of the aorta with respect to the carotids, is associated with microvascular brain damage (visible as WMH) and reduced cognitive performance.[24] In a separate study that employed internal carotid artery velocity measurements, evidence was similarly found for an indirect link between blood

pressure and WMH through a shared coassociation with increasing arterial stiffness.[25] Apart from giving rise to SVD, increased capillary pulsations in the brain could also provide an explanation for widening of the ventricles. These pulsations are transferred to the intracranial CSF, presumably at the site of the choroid plexus where they cause a pulsatile increase in intraventricular CSF pressure during each systole.[22] Increased intraventricular CSF pressure waves could cause an increased transmantle pressure gradient, giving rise to higher pressure waves at the periventricular than at the more superficial brain structures. This gradient may lead to enlargement of the ventricular volume through the so-called waterhammer effect, that continuously pushes the ventricular wall outward, ultimately causing ventricular dilatation.[26] As the ventricles expand, forcing the brain out against the inner table of the calvarium, the sulci may decrease in size along with an increase of the ventricular volume. It is also conceivable that WMH and widening of the ventricles are not just epiphenomena of systemic arterial disease, but that they influence each other. MR-pathological studies have found that periventricular venous collagenosis - a gradual thickening of the walls of periventricular veins and venules with collagen occurring in normal aging - is increased in brains with WMH.[27] In addition to venous collagenosis, MR-pathological studies have found arteriolar tortuosity and reduced vessel density in periventricular WMH.[28] MR elastography has found softening of the brain in NPH patients, that was even more pronounced in the periventricular region[29] and that partly decreased after shunt placement.[30] Though no direct relationship with microvascular changes in the periventricular white matter was implied, it is a theoretical possibility that brains with impaired periventricular white matter will be less able to absorb the systolic pressure waves in the ventricles, resulting in more rapidly increasing and higher – and potentially more damaging – CSF pressure waves during each systole.

The strength of our study includes the nature of the study population, which consists of a cohort of participants in a broad range of age groups, with both clinical and subclinical disease. The study is limited by the absence of participants with significant infarcts, who were excluded to prevent misinterpretation of ventricular and sulcal CSF volumes in our automated segmentation procedure. The group of excluded subjects was relatively older and contained a higher percentage of males and subjects with coronary heart disease and diabetes mellitus. The lack of an independent association in the current study of any cardiovascular risk factor with VV/SV - seeming to refute our hypothesis that ventricular enlargement reflects small vessel disease - may be explained by this truncation. It is possible that inclusion of participants carrying the highest rate of cardiovascular risk factors would have strongly contributed to our findings. Conversely, the fact that the associations described in the current study were observed in younger persons without significant infarcts strengthens our conclusions. An additional

limitation is the lack of measures of intra- or extracranial arterial stiffness, which could provide more direct evidence of the potential contribution of arterial stiffness to ventricular dilatation.

In conclusion, our findings suggest that dilatation of the cerebral ventricles in patients with WMH may not be a mere reflection of SVD-based atrophy, but that it could be, at least partly, based on active expansion of the ventricles. This unexpected finding offers a new perspective on the pathophysiology of NPH.

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