Linear vs volume measures of ventricle size

Relation to present and future gait and cognition

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Neurology® 2020;94:e549-e556. doi:10.1212/WNL.00000000000008673

Abstract

Objective

To compare the clinical utility of volume-based ratios with the standard linear ratio of Evans index (EI) by examining their associations with gait, cognition, and other patient and imaging variables.

Methods

From MRI scans of 1,774 participants in the Mayo Clinic Study of Aging, we calculated 3 ventricle size measures: Evan index (frontal horn width divided by widest width of skull inner table), total ventricular volume, and frontal horn volume as ratios of total intracranial volume. Gait was measured by a timed 25-foot walk and cognition by a composite of psychometric tests. We also evaluated variables associated with the measures of ventricular size. Further, we evaluated gait and cognition associations with MRI of extraventricular findings seen in normal-pressure hydrocephalus: disproportionate enlargement of subarachnoid space (DESH) and focal sulcal dilations (FSD).

Results

Ventricular volume measures had stronger association with gait and cognition measures than EI. In decreasing order of strength of association with ventricle size were DESH, FSD, white matter hyperintensity volume ratio, age, male sex, cortical thickness, and education. Modest evidence was observed that FSD was associated with future decline in gait and cognition.

Conclusion

Ventricular volume measures are clinically more useful than EI in indicating current and future gait and cognition. Multiple factors are associated with ventricle volume size, including FSD and DESH, suggesting that changes in CSF dynamics may go beyond simple ventriculomegaly.

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Abstract presented at the 10th Meeting of the International Society for Hydrocephalus and Cerebrospinal Fluid Disorders, Bologna, Italy, October 19–22, 2018.

Go to [Neurology.org/N](https://www.neurology.org/N) for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

CI = confidence interval; **DESH** = disproportionately enlarged subarachnoid hydrocephalus; **EI** = Evans index; **FH** = frontal horn; **FHVR** = ratio of frontal horn volume to total intracranial volume; **FSD** = focal sulcal dilation; **MCALT** = Mayo Clinic Adult Lifespan Template; **MCSA** = Mayo Clinic Study of Aging; **NPH** = normal-pressure hydrocephalus; **TV** = total ventricular; **TVVR** = ratio of total ventricular volume to total intracranial volume; **WMHV** = white matter hyperintensity volume; **WMHVR** = white matter hyperintensity volume as a ratio of white matter volume.

An increase in ventricle size is associated with age, sex,^{1–3} degenerative brain disease,^{4,5} CSF absorption impairment,⁶ and vascular risk factors.^{7,8} An association between increased ventricle size and gait decline was first recognized in 1982.⁹ A clinically relevant measure of ventricle size would be associated with gait, cognition, or both, cross-sectionally or longitudinally. Evans index (EI), a linear ratio of frontal horn (FH) width to the widest width of skull inner table, is a measure of FH size that has been used in epidemiology studies of idiopathic normal-pressure hydrocephalus (NPH).¹⁰ An EI >0.3 is considered indicative of ventriculomegaly.¹¹ With respect to the general population, in a group of healthy elderly persons, 29% (n = 308) had an EI >0.3, which occurred more often in older vs younger patients and in men vs women.¹² The ratio of ventricular volume to intracranial volume has been proposed as an improved measure of ventricle size, although this ratio has not correlated well with EI.¹³ In the present study, we compared the relationship of EI, the total ventricular (TV) volume/total intracranial volume (TVVR), and the FH volume/total intracranial volume (FHVR) with the baseline and longitudinal gait and cognition measures. The goal was to assess whether TVVR or FHVR, or both, may be more clinically useful in the general population than EI because they may be more strongly associated with clinically relevant variables and outcomes. Our second aim was to identify variables associated with ventricle size, to confirm and expand on prior known associations. The considered variables were age, sex, education, *APOE*, vascular risk factors, white matter hyperintensities,¹⁴ cortical thickness, and extraventricular MRI findings typically associated with NPH, such as focal sulcal dilation (FSD) and disproportionately enlarged subarachnoid hydrocephalus (DESH).¹⁵ The latter is indicated by presence of high tight sulci and enlarged Sylvian fissures. Finally, we evaluated whether these extraventricular MRI findings were associated with gait and cognition.

Methods

Population

We used the resources of the Mayo Clinic Study of Aging (MCSA) for the present study. The MCSA is a community-based longitudinal study of persons without dementia who were recruited at age 70–89 years in Olmsted County, Minnesota. Its details have been described previously.¹⁶ In brief, the volunteer participants are seen approximately once every 15 months, when their gait and cognition are assessed. They also are invited to undergo MRI.

Standard protocol approvals, registrations, and patient consents

The study protocols were approved by the Mayo Clinic and Olmsted Medical Center institutional review boards. All participants provided signed informed consent.

Gait

The participants underwent a timed 25-foot walk at each visit. Later in the study, they also had the more comprehensive assessments of GAITRite (CIR Systems, Inc., Franklin, NJ).¹⁷ Because the GAITRite measures were not available for almost 50% of participants, we focused on the timed walk as our primary measure of gait.

Cognition

All volunteers underwent a full neurologic evaluation and a battery of neuropsychology tests, including subtests of Wechsler Adult Intelligence Scale–Revised¹⁸ and Wechsler Memory Scale–Revised.¹⁹ These and other tests evaluated 4 cognitive areas: executive function (Trail-Making Test B²⁰ and Digit Substitution Test¹⁸), language (Boston Naming Test²¹ and Category Fluency Test²²), memory (Logical Memory II test,¹⁹ Visual Reproduction II subtest,¹⁹ and Rey Auditory Verbal Learning Test²³ [all tests for delayed recall]), and visuospatial capability (Picture Completion and Block Design¹⁹). Scores were combined into a global cognitive score expressed as a Z score,²⁴ which was our primary measure of cognition.

Vascular risk factors

The following vascular risk factors were obtained through nurse abstraction as previously reported^{25–29}: peripheral vascular disease, type 2 diabetes mellitus, hypertension, dyslipidemia, atrial fibrillation, stroke, congestive heart failure, coronary artery disease, obesity, and midlife hypertension. We used a modified version of the overall vascular disease burden score that combined all risk factors as our primary measure. This version was modified from the score described in prior work³⁰ to include midlife hypertension.

MRI studies

MRI were acquired and processed as described previously.³¹ We examined fluid-attenuated inversion recovery images from the initial MRI studies. Each scan was reviewed and markers were manually placed in identification of the widest part of FHs and the widest part of the inner table of the skull. EI was calculated as the ratio of the distance between the markers indicative of the FH width to the distance between those markers indicative of the inner table of the skull.

In addition to the manual EI measures, we performed fully automated measures of TV and FH volume as a ratio of intracranial volume (TVVR and FHVR). We included FHVR in addition to TVVR because EI is a measure of FH. In addition, gait is a key outcome and the FH is surrounded by motor pathways (anterior internal capsule and genu), subcortical motor structures (caudate nucleus), and pathways to and from motor cortices (premotor and supplementary cortices).

For the FH, we divided the lateral ventricles into anterior and posterior sections by creating a dividing plane in the Mayo Clinic Adult Lifespan Template (MCALT) and associated atlas MRI space. The dividing plane in MCALT atlas space was defined with 1 point on the anterior edge of the foramen of Monro and 2 points on the anterior edge of the motor strip near the top of the brain but well off the midline.

As part of our standard T1-weighted image processing pipeline, a warping from MCALT space to subject space was created with advanced normalization tools.³¹ In addition, the lateral ventricles were automatically segmented. We applied the advanced normalization tools–based transformation to move the dividing plane from the template space into the subject space of each participant. The FH volume was measured as the volume of the ventricle compartment anterior to the dividing plane.

We similarly have an automated measure of TVV as a ratio of the total intracranial volume (TVVR).

When reviewing each scan, 1 neurologist (N.R.G.-R.) noted which patients had 2 characteristic features (high tight sulci and enlarged Sylvian fissures) of DESH,¹⁵ now recognized as an extraventricular radiologic factor in idiopathic NPH and included in the Japanese guidelines for treating idiopathic NPH.³¹ We also identified the patients with FSD, another feature of extraventricular hydrocephalus.³² Because white matter changes may be associated with gait and cognition, the white matter hyperintensity volume (WMHV) was measured with a method described previously.³³

Degenerative diseases such as Alzheimer disease affect the FH, body, temporal horn, and occipital horn of the ventricle,⁵ so we included cortical thickness to account for degenerative disease.³¹

Statistical analysis

For all analyses, gait speed, EI, FHVR, and TVVR were log-transformed. Associations involving continuous variables were expressed in relation to a difference equal to the interquartile range of baseline measures. For cross-sectional association analyses with use of baseline data, we used linear regression for continuous outcome variables (e.g., ventricle size, gait, cognition) and logistic regression for binary

Table 1 Patient baseline characteristics

Characteristics	No. of patients	Value, median (IQR) or n (%)
Female sex	1,774	841 (47)
Age, y	1,774	78 (74 to 82)
Education, y	1,774	13 (12–16)
APOE ε4 carrier	1,769	473 (27)
Diagnosis of mild cognitive impairment	1,774	266 (15)
Cognition	1,667	0.35 (–0.32 to 0.98)
Gait speed, cm/s	1,659	108.9 (95.3 to 127.0)
Vascular disease burden score	1,764	3 (2 to 4)
Peripheral vascular disease	1,773	542 (31)
Type 2 diabetes mellitus	1,772	313 (18)
Hypertension	1,770	1,346 (76)
Dyslipidemia	1,770	1,477 (83)
Atrial fibrillation	1,770	246 (14)
Congestive heart failure	1,769	133 (8)
Stroke	1,770	89 (5)
Coronary artery disease	1,772	432 (24)
Obesity	1,769	554 (31)
Midlife hypertension	1,772	616 (35)
MRI		
Evans index, %	1,494	27.4 (25.2 to 29.5)
FHVR, %	1,774	1.13 (0.86 to 1.47)
TVVR, %	1,774	3.13 (2.44 to 4.09)
WMHVR, %	1,501	1.95 (1.28 to 3.46)
Cortical thickness	1,763	2.78 (2.68 to 3.19)
Focal sulcal dilation	1,493	50 (3)
DESH	1,451	100 (7)

Abbreviations: DESH = disproportionately enlarged subarachnoid hydrocephalus (tight convexity or enlarged Sylvian fissures); FHVR = ratio of frontal horn volume to total intracranial volume; IQR = interquartile range; TVVR = ratio of total ventricular volume to total intracranial volume; WMHVR = white matter hyperintensity volume as a ratio of white matter volume.

variables (e.g., NPH imaging variables, ventricle size above or below a cut point). We used mixed-effects models for associations of baseline variables with trajectory of gait and cognition. The longitudinal analyses used all available measures of gait or cognition, incorporating random

Figure Ventricle size: Total ventricle volume ratio vs Evans index

participant effects for intercepts and slopes (trajectories) over time. The intercepts and the slopes (trajectories) were modeled as linear combinations of baseline participant characteristics. All regression-based analyses were adjusted for age and sex, with additional variables adjusted for as indicated. When fitted values were obtained from models, these refer to a hypothetical “average” participant, one with variables set equal to mean levels across all.

Data availability

Data may be made available after a reasonable and well-motivated request to the principal investigator of MCSA, Dr. Ronald C. Petersen. Data cannot, however, be made freely available to the public, due to privacy regulations and informed consent.

Results

Participant characteristics

The median age of the 1,774 study participants at baseline was 78 years; 47% were women, 27% were *APOE* ε4 gene carriers, and 15% had a diagnosis of mild cognitive impairment (table 1). Although the volume-based measure of TVVR was correlated with the EI as expected (figure), the correspondence was not high ($R^2 = 0.37$), and similarly for FHVR. We noted that the typically used EI cutoff of 0.30 resulted in an 80%:20% split of patients with EI measures. Thus, for comparison, we identified the corresponding cutoffs for TVVR and FHVR that divided the same set of study participants in the same proportion; these were 0.0405 for TVVR and 0.0143 for FVHR.

Association of ventricle size with gait and cognition

The 2 volume measures were more strongly associated with gait and cognition both cross-sectionally and longitudinally than EI in analyses adjusting for age and sex (table 2). Similar analyses with use of scores for the separate cognitive domains showed that ventricle size had strongest estimated associations with attention and memory domains at baseline and had stronger associations with change in attention and language domains. Through examination of the ventricle size measures as binary variables according to the cutoffs defined above, we obtained fitted gait and cognition and their trajectories when the levels were high vs low for each. Those with low TVVR had a fitted mean gait of 107 cm/s (95% confidence interval [CI] 106–108 cm/s) with subsequent estimated decline over 5 years of 12% (95% CI 11%–13%). Those with high TVVR started out with a slower gait of 100 cm/s (95% CI 98–103 cm/s) and had a more extreme estimate of subsequent decline of 16% (95% CI 14%–18%). When examining low vs high values of TVVR and EI in combination (table 3 and figure), we saw even more clearly that the TVVR was more discriminatory than the EI. In particular, among patients with low

Table 2 Associations of ventricle size measures with gait and cognition

Measure ^{a,b}	Baseline		Trajectory ^c	
	Estimate (95% CI)	p Value	Estimate (95% CI)	p Value
Timed 25-foot walk, %^d				
EI	−0.58 (−1.30 to 0.14)	0.11	−0.01 (−0.70 to 0.69)	0.99
FHVR	−3.84 (−5.44 to −2.22)	<0.001	−3.04 (−4.61 to −1.45)	<0.001
TVVR	−4.07 (−5.67 to −2.44)	<0.001	−3.71 (−5.29 to −2.10)	<0.001
Cognition				
EI	0.000 (−0.028 to 0.027)	0.97	−0.028 (−0.050 to −0.007)	0.009
FHVR	−0.212 (−0.277 to −0.147)	<0.001	−0.136 (−0.185 to −0.086)	<0.001
TVVR	−0.251 (−0.316 to −0.187)	<0.001	−0.160 (−0.209 to −0.110)	<0.001

Abbreviations: CI = confidence interval; EI = Evans index; FHVR = ratio of frontal horn volume to total intracranial volume; TVVR = ratio of total ventricle volume to total intracranial volume.

^a Associations with baseline gait and cognition were estimated from linear regression models with adjustment for age and sex.

^b Associations with gait and cognition trajectories were estimated from linear mixed-effects regression models with adjustment for age and sex.

^c Trajectories were based on a 5-year period.

^d Gait speed was transformed on the natural logarithm scale; therefore, the estimates (%) were calculated as $100 \times (e^{\beta} - 1)$.

Table 3 Associations of binary measures of ventricle size with gait and cognition

Measure ^a	Baseline ^{b,c}	<i>p</i> Value ^e	Trajectory ^{b-d}	<i>p</i> Value ^e
	Fitted gait/cognition at baseline (95% CI)		Fitted change over 5 y (absolute for cognition, % for gait) (95% CI)	
Timed 25-ft walk, cm/s ^f				
Low TVVR and low EI	107.9 (106.3 to 109.4)	Ref	−11.63 (−12.77 to −10.48)	Ref
Low TVVR and high EI	105.3 (101.2 to 109.5)	0.26	−9.02 (−12.09 to −5.84)	0.12
High TVVR and low EI	100.1 (96.1 to 104.3)	<0.001	−15.76 (−19.23 to −12.14)	0.03
High TVVR and high EI	101.2 (97.4 to 105.1)	0.002	−15.60 (−18.79 to −12.28)	0.03
Cognition, Z score				
Low TVVR and low EI	0.382 (0.327 to 0.437)	Ref	−0.387 (−0.427 to −0.346)	Ref
Low TVVR and high EI	0.408 (0.255 to 0.562)	0.75	−0.314 (−0.425 to −0.203)	0.23
High TVVR and low EI	0.070 (−0.084 to 0.224)	<0.001	−0.574 (−0.695 to −0.453)	0.004
High TVVR and high EI	0.124 (−0.019 to 0.267)	0.001	−0.597 (−0.710 to −0.484)	<0.001

Abbreviations: CI = confidence interval; EI = Evans index; FHVR = ratio of frontal horn volume to total intracranial volume; Ref = reference; TVVR = ratio of total ventricular volume to total intracranial volume.

^a Associations with baseline gait and cognition were estimated from linear regression models with adjustment for age and sex.

^b Fitted baseline values and changes in each subgroup refer to those for a hypothetical individual with mean values of the covariates age and sex.

^c Associations with gait and cognition trajectories were estimated from linear mixed-effects regression models with adjustment for age and sex.

^d Trajectories were based on a 5-year period. High values of each of the measures were defined here as EI > 0.30, FHVR > 0.0143, and TVVR > 0.0405.

^e *p* Values refer to comparison with corresponding low-low group.

^f Gait speed was transformed on the natural logarithm scale; therefore, the changes (%) were calculated as 100*(e^β − 1).

TVVR, whether EI was high or low had little effect on gait and cognition; the same was true for those with high TVVR. Yet, among those with low EI, whether TVVR was high did have an effect, similarly for those with high EI.

Other variables with strong evidence of association with gait and cognition, even after adjustment for other variables,

were years of education (gait and cognition at baseline), APOE ε4 (cognition at baseline and trajectory), vascular disease burden (gait at baseline), WMHV as a ratio of white matter volume (WMHVR) (gait at baseline, cognition at baseline, and trajectory), and cortical thickness (gait trajectory, cognition at baseline, and trajectory). Although adjustment for variables in addition to age and sex attenuated

Table 4 Associations of patient characteristics with total ventricle volume ratio (% effect on volume)

Characteristic	Adjusted for age and sex only		Adjusted for all other variables ^a	
	Estimate (95% CI)	<i>p</i> Value	Estimate (95% CI)	<i>p</i> Value
Male sex	12.44 (8.89 to 16.10)	<0.001	8.05 (4.70 to 11.51)	<0.001
Age, IQR (+8 y)	23.07 (20.15 to 26.06)	<0.001	11.02 (8.07 to 14.05)	<0.001
Education, IQR (+4 y)	2.52 (0.24 to 4.86)	0.03	2.64 (0.42 to 4.92)	0.02
APOE ε4 carrier	−0.44 (−3.99 to 3.23)	0.81	−0.02 (−3.44 to 3.54)	0.99
Vascular disease burden score, IQR (+2 U)	2.41 (0.58 to 4.28)	<0.01	0.31 (−1.50 to 2.14)	0.74
WMHVR, IQR (×2.70)	19.78 (16.98 to 22.64)	<0.001	14.20 (11.45 to 17.03)	<0.001
Cortical thickness, IQR (×1.19)	−11.66 (−13.45 to −9.83)	<0.001	−6.46 (−8.48 to −4.39)	<0.001
Focal sulcal dilation	60.65 (47.29 to 75.23)	<0.001	44.62 (32.13 to 58.28)	<0.001
DESH	53.98 (44.85 to 63.68)	<0.001	40.59 (32.17 to 49.53)	<0.001

Abbreviations: CI = confidence interval; DESH = disproportionately enlarged subarachnoid hydrocephalus (tight convexity or enlarged Sylvian fissures); IQR = interquartile range; WMHVR = white matter hyperintensity volume as a ratio of white matter volume.

^a Analyses adjusted for all of the above variables. As an exception, focal sulcal dilation was not adjusted for DESH and vice versa to aid interpretation because most patients with focal sulcal dilation also had DESH.

Table 5 Associations of focal sulcal dilation and DESH with gait and cognition

Variable of interest adjusted for ^a	Baseline		Trajectory ^b	
	Estimate (95% CI)	p Value	Estimate (95% CI)	p Value
Gait speed (timed 25-ft walk), % difference or change^{c,d}				
Focal sulcal dilation				
Age and sex only	−2.10 (−8.84 to 5.13)	0.56	−7.53 (−13.83 to −0.77)	0.03
Multiple variables	−0.64 (−8.10 to 7.42)	0.87	−7.56 (−14.22 to −0.39)	0.04
+EI	0.80 (−6.81 to 9.04)	0.84	−8.28 (−14.94 to −1.10)	0.02
+FHVR	0.51 (−7.14 to 8.79)	0.90	−7.48 (−14.25 to −0.17)	0.05
+TVVR	0.76 (−6.96 to 9.13)	0.85	−7.06 (−13.89 to 0.30)	0.06
DESH				
Age and sex only	−1.85 (−6.69 to 3.23)	0.47	−1.30 (−5.89 to 3.50)	0.59
Multiple variables	1.12 (−4.10 to 6.62)	0.68	−0.45 (−5.10 to 4.42)	0.85
+EI	2.37 (−2.96 to 8.00)	0.39	−0.99 (−5.66 to 3.91)	0.69
+FHVR	2.50 (−2.95 to 8.25)	0.38	−0.41 (−5.22 to 4.65)	0.87
+TVVR	2.97 (−2.57 to 8.82)	0.30	0.21 (−4.72 to 5.40)	0.94
Cognition^c				
Focal sulcal dilation				
Age and sex only	−0.285 (−0.543 to −0.027)	0.03	−0.269 (−0.469 to −0.069)	0.008
Multiple variables	−0.177 (−0.440 to 0.086)	0.19	−0.201 (−0.417 to 0.014)	0.07
+EI	−0.157 (−0.422 to 0.109)	0.25	−0.194 (−0.411 to 0.024)	0.08
+FHVR	−0.095 (−0.361 to 0.171)	0.48	−0.185 (−0.404 to 0.034)	0.10
+TVVR	−0.044 (−0.312 to 0.224)	0.75	−0.169 (−0.389 to 0.051)	0.13
DESH				
Age and sex only	0.005 (−0.182 to 0.192)	0.96	−0.102 (−0.247 to 0.043)	0.17
Multiple variables	0.079 (−0.103 to 0.261)	0.40	0.017 (−0.131 to 0.165)	0.82
+EI	0.095 (−0.089 to 0.280)	0.31	0.029 (−0.121 to 0.178)	0.71
+FHVR	0.160 (−0.028 to 0.348)	0.09	0.047 (−0.105 to 0.199)	0.54
+TVVR	0.207 (0.018 to 0.397)	0.03	0.064 (−0.090 to 0.218)	0.41

Abbreviations: CI = confidence interval; DESH = disproportionately enlarged subarachnoid hydrocephalus (tight convexity or enlarged Sylvian fissures); EI = Evans index; FHVR = ratio of frontal horn volume to total intracranial volume; TVVR = ratio of total ventricle volume to total intracranial volume, WMHVR = white matter hyperintensity volume as a ratio of white matter volume.

^a The multiple variables for adjustments were age, sex, education, *APOE* ε4, vascular disease burden, WMHVR, and cortical thickness.

^b Associations with gait and cognition trajectories were estimated from linear mixed-effects regression models.

^c Associations with baseline gait and cognition were estimated from linear regression models.

^d Gait speed was transformed on the natural logarithm scale; therefore, the estimates (%) were calculated as $100 \times (e^{\text{coefficient}} - 1)$.

the estimated associations of ventricle size with gait and cognition, there was still a strong association of TVVR with cognition at baseline (−0.179 [95% CI −0.264 to −0.094]; $p < 0.001$), and some moderate but significant evidence of association of TVVR with cognition trajectory (−0.067 [95% CI −0.134 to −0.001]; $p = 0.05$), and with gait at baseline (−2.59 [95% CI −4.87 to −0.25]; $p = 0.03$).

Association of variables with ventricle size

Our findings in order of the strongest to the weakest evidence of association with ventricle size were DESH, FSD, WMHVR, age, male sex, cortical thickness (negatively associated), and years of education (table 4). Both FSD and DESH were estimated to be associated with a >30% increase in ventricle size. Vascular disease risk burden, while statistically significant in

the analysis adjusted only for age and sex, did not show evidence of association after adjustment for other variables.

Association of NPH imaging characteristics with gait and cognition

Finally, we demonstrated that MRI findings typical of extraventricular NPH (DESH and FSD) were strongly associated with ventricle size and thus to some extent indirectly related to gait and cognition through ventricle size. Yet, we sought to assess whether they were related more directly. After adjustment for age and sex only, there was evidence of association of FSD with cognition at baseline and its trajectory and marginal evidence of association of FSD with gait trajectory (table 5). After adjustment for other variables, marginal evidence association of FSD with gait trajectory remained. This observation was despite only 50 persons having FSD. When controlling for ventricle size, there was no evidence of association of DESH with worsened gait or cognition, regardless of whether adjustment was made for other variables.

Discussion

In the MCSA, a volumetric measure of ventricle size (TVVR or FHVR) in comparison with EI is more strongly associated with baseline and longitudinal gait and cognitive measures. These volume measures can be generated automatically. Inclusion of one or both of these measures on MRI reports would allow a clinician to be more objective in the determination of whether the ventricles are large. Further, if a clinician who was reviewing an MRI had the information that the TVVR or the FHVR was in the top 20%, then the clinician would know that (1) the patient's gait and cognition are both likely diminished compared with a person with ventricle size in the lower 80% and (2) gait and cognition are at risk of more rapid decline over the next few years.

The second important result in this study is the finding of strong associations of various factors with ventricle size. In order of the strongest to the weakest, they are DESH, FSD, WMHVR, age, male sex, cortical thickness, and education. It is remarkable how strong the associations with DESH and FSD are despite being present in only 7% and 3%, respectively, of study participants. These associations suggest that in an unselected elderly population, ventricular enlargement is not an isolated phenomenon but rather is associated with prominent changes in CSF-containing extraventricular structures. Thus, the underlying alteration in CSF dynamics affects not only ventricular expansion but also dilation of certain sulci and fissures combined with obliteration of others. Although this was not a study of NPH, the findings suggest that alterations in CSF dynamics are far more than large ventricles. In an NPH population, these factors are likely to be the dominant factors correlated with ventricle size, and this needs to be studied. Vascular risk burden showed evidence of association with ventricle size when adjustment was made for only age and sex; it no longer did so with adjustment for a greater number of variables. However, vascular risk factor burden is related to variables such as WMHVR that were adjusted in the multivariable models.

Third, we looked at MRI extraventricular findings associated with NPH in relation to gait and cognition. Modest evidence showed that FSD was associated with future decline in both gait and cognition, although no association of DESH with gait and cognition was observed.

Limitations of the present study include the relatively low number of persons with extraventricular NPH-related findings on MRI. This would have limited our power to show the effects of these features in an NPH population. However, this study is still valuable in showing its role in a large community-based population. When applied to an NPH population, the features of ventricle size, DESH, and FSD would be of interest.

We report evidence that in the context of clinical use, the volume-based measures of ventricle size, TVVR, and FHVR are more informative than the linear measure of EI. Furthermore, these measurements can be automated. Multiple factors are associated with ventricle volume size, including FSD and DESH. The strong association of ventricular volume with extraventricular structural imaging changes in CSF-containing structures suggests that changes in CSF dynamics go well beyond simple ventriculomegaly.

Study funding

Supported by the NIH (U01 AG006786, R01 AG011378, R01 AG041851, P50 AG44170, RF1 AG55151, and R01 AG049704) and the Robert H. and Clarice Smith and Abigail van Buren Alzheimer's Disease Research Program. This study was made possible by the Rochester Epidemiology Project (R01 AG034676). It also was partially funded by the David Eisenberg Endowed Chair at Mayo Clinic. The content is solely the responsibility of the authors and does not necessarily represent the official views of NIH.

Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Publication history

Received by *Neurology* December 28, 2018. Accepted in final form July 31, 2019.

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Continued

Appendix (continued)

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