Vascular risk factors in INPH

A prospective case-control study (the INPH-CRasH study)

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ABSTRACT

Objective: To assess the complete vascular risk factor (VRF) profile of idiopathic normal pressure hydrocephalus (INPH) using a large sample of representative patients with INPH and population-based controls to determine the extent to which vascular disease influences INPH pathophysiology.

Methods: All patients with INPH who underwent shunting in Sweden in 2008–2010 were compared to age- and sex-matched population-based controls. Inclusion criteria were age 60–85 years and no dementia. The 10 most important VRFs and cerebrovascular and peripheral vascular disease were prospectively assessed using blood samples, clinical examinations, and standardized questionnaires. Assessed VRFs were hypertension, hyperlipidemia, diabetes, obesity, psychosocial factors, smoking habits, diet, alcohol intake, cardiac disease, and physical activity.

Results: In total, 176 patients with INPH and 368 controls participated. Multivariable logistic regression analysis indicated that hyperlipidemia (odds ratio [OR] 2.380; 95% confidence interval [CI] 1.434–3.950), diabetes (OR 2.169; 95% CI 1.195–3.938), obesity (OR 5.428; 95% CI 2.502–11.772), and psychosocial factors (OR 5.343; 95% CI 3.219–8.868) were independently associated with INPH. Hypertension, physical inactivity, and cerebrovascular and peripheral vascular disease were also overrepresented in INPH. Moderate alcohol intake and physical activity were overrepresented among the controls. The population-attributable risk percentage was 24%.

Conclusions: Our findings confirm that patients with INPH have more VRFs and lack the protective factors present in the general population. Almost 25% of cases of INPH may be explained by VRFs. This suggests that INPH may be a subtype of vascular dementia. Targeted interventions against modifiable VRFs are likely to have beneficial effects on INPH. *Neurology*® 2017;88:577–585

GLOSSARY

BMI = body mass index; **CI** = confidence interval; **CRasH** = Comorbidity and Risk Factors Associated With Hydrocephalus; **CVD** = cerebrovascular disease; **INPH** = idiopathic normal pressure hydrocephalus; **LVD** = large vessel disease; **MMSE** = Mini-Mental State Examination; **OR** = odds ratio; **PAR%** = population-attributable risk percent; **PVD** = peripheral vascular disease; **SHQR** = Swedish Hydrocephalus Quality Registry; **SPR** = Swedish population register; **SVD** = small vessel disease; **VaD** = vascular dementia; **VaDis** = vascular disease; **VRF** = vascular risk factor.

Idiopathic normal pressure hydrocephalus (INPH) is a surgically treatable cause of dementia and is characterized by ventriculomegaly, gait disturbances, cognitive decline, and urinary symptoms.^{1,2} The underlying causes of INPH are largely unknown. The clinical picture resembles that of subcortical atherosclerotic encephalopathy or Binswanger disease.^{3,4} An emerging concept is that the pathophysiology of INPH is multifactorial and that the well-described CSF hydrodynamic dysfunction in INPH may be combined with subcortical vascular dementia (VaD).^{1,3–8} If INPH is a subtype of VaD, vascular risk factor (VRF) management may be beneficial for the treatment of patients with INPH. This would be an additional noninvasive treatment option for patients with INPH.

Supplemental data
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(A) Patient flow diagram. (B) Control flow diagram. INPH = idiopathic normal pressure hydrocephalus; MMSE = Mini-Mental State examination.

INTERHEART⁹ and INTERSTROKE¹⁰ are 2 of the largest population-based VRF studies. These studies have proven that 9 and 10 VRFs, respectively, account for 90% of all myocardial infarctions and strokes. There are no similar studies combining multiple VRFs in patients with INPH. Hypertension is perhaps the most important VRF for INPH,³ and cerebrovascular disease (CVD) (e.g., stroke and white matter hyperintensities) is frequently comorbid with INPH.^{3–5} There are indications that other VRFs, such as diabetes and cardiac disease, may be overrepresented in INPH.^{11–15} However, existing studies are small and have several methodologic limitations.

The INPH–Comorbidity and Risk Factors Associated With Hydrocephalus (CRasH) study is a large, prospective, case-control study comparing all patients with INPH who have

undergone shunting in Sweden between 2008 and 2010 to population-based controls.⁸ The hypothesis for the study was that VRFs and subsequent vascular disease (VaDis) are overrepresented in INPH. The objective was to assess the total VRF profile in definitive cases of INPH and to determine the extent to which VaDis influences INPH pathophysiology.

METHODS In the INPH-CRasH study, VRFs and VaDis in 176 consecutive patients with INPH who had undergone shunting were compared to those in 368 age- and sex-matched population-based controls. The participants completed an extensive questionnaire, had a standardized visit to their health care provider, and donated a blood sample.

Identification of study participants. Patients with INPH were identified through the Swedish Hydrocephalus Quality Registry (SHQR), where all adult (≥ 18 years) individuals who have undergone shunting due to hydrocephalus in Sweden are registered. During the study period, the registry covered 5 of 6 neurosurgical units (referral area for 80% of the Swedish population). The data used from the SHQR were as follows: date of birth, sex,

Table 1 Complete vascular risk factor profile for patients with idiopathic normal pressure hydrocephalus (INPH) and the general population

Risk factor	Frequency of each variable, % (no. of each variable/total no. of probands within each variable)		Crude OR (95% CI)	p Value	Adjusted ^a OR (95% CI)	p Value
	INPH	Controls				
Hypertension	83.4 (131/157)	74.7 (263/352)	1.705 (1.050-2.768)	0.031	1.656 (1.017-2.697)	0.043
Hyperlipidemia	37.1 (52/140)	19.4 (63/325)	2.457 (1.583-3.814)	<0.001	2.508 (1.610-3.904)	<0.001
Diabetes	26.8 (38/142)	13.1 (44/337)	2.433 (1.493-3.965)	<0.001	2.420 (1.476-3.969)	<0.001
Abdominal obesity (WTH)	91.4 (128/140)	72.6 (236/325)	4.023 (2.121-7.629)	<0.001	5.698 (2.849-11.397)	<0.001
Smoking	55.2 (95/172)	52.1 (190/365)	1.136 (0.790-1.635)	0.491	1.227 (0.843-1.785)	0.286
Physical activity						
Physically active	33.1 (53/160)	51.1 (186/364)	0.474 (0.322-0.699)	<0.001	0.482 (0.326-0.714)	<0.001
Physically inactive	24.1 (40/166)	9.5 (35/367)	3.011 (1.830-4.954)	<0.001	2.840 (1.709-4.719)	<0.001
Psychosocial factors	48.3 (83/172)	15.6 (57/365)	5.039 (3.339-7.064)	<0.001	4.920 (3.243-7.464)	<0.001
Cardiac disease						
Ischemic heart disease	23.2 (32/138)	21.0 (70/333)	1.134 (0.705-1.824)	0.478	1.118 (0.687-1.819)	0.654
All cardiac disease	45.5 (65/143)	41.1 (140/341)	1.196 (0.807-1.773)	0.372	1.175 (0.777-1.777)	0.444
Alcohol						
Moderate alcohol intake	54.1 (92/170)	67.4 (246/365)	0.571 (0.393-0.828)	0.003	0.607 (0.414-0.889)	0.010
High alcohol intake	20.0 (34/170)	22.7 (83/365)	0.849 (0.552-1.330)	0.476	0.934 (0.587-1.487)	0.773
Diet						
Prudent diet	74.0 (128/173)	75.2 (276/367)	0.938 (0.620-1.419)	0.761	0.930 (0.612-1.414)	0.735
Unhealthy dietary pattern	17.9 (31/173)	16.4 (60/366)	1.113 (0.691-1.794)	0.659	1.085 (0.670-1.758)	0.740

Abbreviations: CI = confidence interval; OR = odds ratio; WTH = waist-to-hip index.

All variables were dichotomous with outcomes of yes or no.

^a Adjusted for age and sex.

INPH diagnosis, date of surgery, and Mini-Mental State Examination (MMSE) score. The controls were identified from the Swedish population register (SPR), where all citizens in Sweden are registered at birth. The data used from the SPR were date of birth and sex.

INPH. The flow diagram for patient recruitment is shown in the figure, A. In total, 396 patients with INPH underwent shunting between 2008 and 2010. The inclusion criteria were as follows: alive in 2011, when the study was conducted; age 60–85 years; and not having dementia (defined as a preoperative MMSE score <23). Of the 239 patients meeting the inclusion criteria, 176 chose to participate (age 74 ± 6 years [mean $\pm$ SD], female patients: 42% [$n = 73$]). Of the patients, 23% ($n = 41$) underwent surgery in 2008, 35% ($n = 61$) underwent surgery in 2009, and 42% ($n = 74$) underwent surgery in 2010.

Controls. The flow diagram for control participant recruitment is shown in the figure, B. The 4 individuals of the same sex born closest in date to each participating patient with INPH were identified. A case-to-control ratio of 1:2 was desirable for statistical analysis. Due to a presumed answer rate of 50% among the controls, 4 controls per case were contacted (except for 5 patients with INPH who were late in confirming their participation in the study). After the exclusion step (same exclusion criteria were used as those used for the patients with INPH), 368 controls participated in the study (age 73 ± 6 years [mean $\pm$ SD], female patients: 37% [$n = 135$]).

Preoperative evaluation. Before surgery, all patients with INPH underwent an evaluation by an INPH team. According to international guidelines,² the diagnosis was based on patient history, neurologic examination, and MRI/CT revealing a communicating hydrocephalus. A CSF tap test or an infusion test was performed according to the standard practice of each center.

Prospective ascertainment of risk factors. First, each participant completed a questionnaire regarding demographics, illnesses, somatic and mental symptoms, medications, and lifestyle, followed by a standardized visit at the nearest health care provider. There, blood samples (analyzed for serum glucose, ApoB, ApoA1, ratio of ApoB to ApoA1, and plasma creatinine), blood pressure (3 measurements taken after a minimum 10-minute rest), ECGs, height, weight, and waist-to-hip ratio⁹ were obtained. The use of lipid-lowering drugs was assessed using the Swedish national drug registry, where all medication prescribed in Sweden is registered. For details regarding each of the VRFs we investigated, see table e-1 at Neurology.org.

Statistical analyses. SPSS-21 (SPSS Inc., Chicago, IL) was used for statistical analysis. Significance was set at 0.05 (2-sided). For categorical variables, logistic regression was used to calculate crude and adjusted (for age and sex) odds ratios (ORs). Analyses of covariance were used for continuous variables (covariates: age and sex). When building the multivariable logistic regression models, manual backwards analysis was used. Only participants who had data for all of the parameters were included. To calculate the population-attributable risk percent (PAR%), the regpar

routine in STATA 13 was used. For comparisons between patients who had their shunt surgeries in each of the 3 years of the study, a χ^2 test and an analysis of variance were used.

When conducting the comparative case-control analyses, the matching requirement was waived for 2 reasons. First, there were 5 patients with INPH whose data arrived at the end of December 2011. Since the recruitment period ended in 2011, these patients did not have individually matched controls. Second, for 33 cases, all controls declined to participate. Strictly matched analyses would have excluded all of these participants from the analyses and valuable information would have been lost. Thus, the findings presented here are obtained from models fit with unconditional logistic regression and adjusted for the matching criteria. This is the same approach used in INTERHEART⁹ and INTERSTROKE.¹⁰

Power calculations performed before the study revealed that with a proposed sample size of 200 cases and 400 controls, the study would have a power of 87.4%, assuming that the mean percentage of participants with hypertension is 45% in patients with INPH¹⁶ and 32% in the general population.¹⁰

Standard protocol approvals, registrations, and patient consents. The INPH-CRasH study was carried out in accordance with the Declaration of Helsinki and was approved by the ethical review board at Umeå University. The study is registered at clinicaltrials.gov (NCT01850914). Participants were informed of the study in a covering letter. Each participant provided informed consent by sending back the filled-in questionnaire.

RESULTS Table 1 summarizes the total VRF profile in patients with INPH and in the controls. After adjustment for age and sex, 6 of 10 VRFs were overrepresented in the INPH group. These VRFs are hypertension, hyperlipidemia, diabetes, abdominal

obesity, physical inactivity, and psychosocial factors. The PAR% obtained using a model containing all 6 VRFs associated with INPH (adjusted for age and sex) was 24% (95% confidence interval [CI] 20%–28%). Two of the 3 protective factors were overrepresented among the controls. These factors were moderate alcohol intake and physical activity.

No participant had all 10 VRFs. The patients with INPH had a higher mean number of VRFs than the controls (4.4 ± 1.5 SD vs 3.3 ± 1.5 SD, $p < 0.001$). Seventy-three percent of the patients had ≥ 4 VRFs. However, only 42.8% of the controls had ≥ 4 VRFs (OR adjusted for age and sex 4.0, 95% CI 2.5–6.6; $p < 0.001$). Higher numbers of VRFs were associated with higher ORs (an increase of ~ 1.6 OR per additional VRF).

Data regarding manifest VaDis are presented in table 2. Peripheral vascular disease (PVD) and CVD were overrepresented in the INPH group; however, ischemic heart disease was not overrepresented. When considering individual components of PVD and CVD, stenosis of extracranial cerebral arteries, kidney disease, and stroke were overrepresented in the INPH group.

When building a multivariable logistic regression model adjusted for age and sex containing the 6 VRFs associated with INPH in combination with PVD and CVD, 4 VRFs remained independently associated with INPH. These VRFs were hyperlipidemia (OR 2.380; 95% CI 1.434–3.950; $p = 0.001$), diabetes (OR 2.169; 95% CI 1.195–3.938; $p = 0.011$),

Table 2 Manifest vascular disease in patients with idiopathic normal pressure hydrocephalus (INPH) and the general population

Variable	Frequency of each variable, % (no. of each variable/total no. of probands)		OR (95% CI)	p Value
	INPH	Controls		
Peripheral vascular disease (any condition mentioned below)	89.5 (128/143)	74.7 (245/328)	2.795 (1.494–5.231)	0.001
Claudicatio intermittens	6.2 (10/162)	3.9 (14/361)	1.640 (0.710–3.785)	0.247
Stenosis of extracranial cerebral arteries	8.7 (14/161)	3.3 (12/361)	2.664 (1.198–5.927)	0.016
Kidney disease (GFR <90)	86.4 (121/140)	73.5 (238/324)	2.209 (1.229–3.969)	0.008
Chronic kidney disease (GFR <60)	17.9 (25/140)	9.3 (30/324)	1.956 (1.075–3.557)	0.028
Cerebrovascular disease (any condition mentioned below)	24.7 (36/146)	13.0 (46/354)	2.139 (1.298–3.525)	0.003
TIA	16.2 (24/148)	10.1 (36/356)	1.667 (0.947–2.934)	0.077
Stroke	15.8 (26/165)	7.8 (28/361)	2.138 (1.197–3.820)	0.010
Ischemic heart disease (any condition mentioned below)	23.2 (32/138)	21.0 (70/333)	1.118 (0.687–1.819)	0.654
Myocardial infarction (as seen on ECG)	9.3 (13/140)	7.1 (23/325)	1.381 (0.675–2.827)	0.377
Myocardial infarction (self-reported)	11.3 (19/168)	12.7 (46/362)	0.859 (0.482–1.531)	0.859
Myocardial infarction (as seen on ECG or self-reported)	21.7 (30/138)	18.7 (62/332)	1.196 (0.726–1.969)	0.482
Left bundle blockage (as seen on ECG)	3.6 (5/140)	3.1 (10/325)	1.133 (0.375–3.419)	0.825
Angina pectoris (self-reported)	13.1 (22/168)	10.8 (39/360)	1.214 (0.692–2.131)	0.498

Abbreviations: CI = confidence interval; GFR = glomerular filtration rate; OR = odds ratio.

All variables were dichotomous with outcomes of yes or no. All ORs were adjusted for age and sex.

Table 3 Lipid profiles of patients with idiopathic normal pressure hydrocephalus (INPH) and the general population

Variable	Value or frequency (%) of each variable (no. of each variable/total no. of the probands)			
	INPH	Controls	OR (95% CI)	p Value
Mean ApoB, g/L	1.123 ± 0.26 SD (140)	1.052 ± 0.26 SD (325)	—	0.007 ^a
High ApoB (>1.2 g/L)	37.9 (53/140)	24.9 (81/325)	1.869 (1.218–2.867)	0.004 ^b
Mean ApoA1, g/L	1.427 ± 0.26 SD (140)	1.517 ± 0.25 SD (325)	—	<0.001 ^a
Low ApoA1 (<1.15 g/L in male patients, <1.25 g/L in female patients)	17.1 (24/140)	5.2 (17/325)	3.725 (1.926–7.206)	<0.001 ^b
Mean ratio of ApoB/ApoA1	0.81 ± 0.25 SD (140)	0.71 ± 0.20 SD (325)	—	<0.001 ^a
High ratio of ApoB/ApoA1 (>0.90 for male patients, >0.80 for female patients)	37.1 (52/140)	19.4 (63/325)	2.508 (1.610–3.904)	<0.001 ^b
Lipid-lowering drugs	6.8 (12/176)	9.8 (36/368)	0.691 (0.349–1.368)	0.289 ^b
High ratio of ApoB/ApoA1 or use of lipid-lowering drugs	43.4 (62/143)	29.3 (96/328)	1.875 (1.245–2.824)	0.003 ^b

Abbreviations: CI = confidence interval; OR = odds ratio.

^aAnalysis of covariance: covariates: age and sex.

^bLogistic regression: ORs adjusted for age and sex.

abdominal obesity (OR 5.428; 95% CI 2.502–11.772; $p < 0.001$), and psychosocial factors (OR 5.343; 95% CI 3.219–8.868; $p < 0.001$).

Table 3 summarizes data regarding the lipid profiles of patients with INPH and controls. Patients with INPH had higher levels of disease-associated apolipoproteins (ApoB) and lower levels of protective apolipoproteins (ApoA1) than controls in all comparisons. However, there was no difference between the 2 groups in the use of lipid-lowering drugs. For details regarding obesity in patients with INPH, see table 4. More patients were obese than controls, both when considering general obesity (measured by body mass index [BMI]) and abdominal obesity (measured by waist-to-hip ratio). For details regarding blood pressure and hypertension, see table e-2.

There was no difference among patients with INPH who had their surgeries in the 3 different years in any of the measures, except for high alcohol intake. More patients from 2009 had a high alcohol intake

when compared to patients from 2010 (32.2% vs 12.5%, $p = 0.006$).

DISCUSSION The INPH-CRasH study has an appropriate design, large sample sizes, and representative cases and controls, and uses a modern epidemiologic view regarding VRFs. The entire VRF profile was investigated. Our data indicate that patients with INPH have a greater VRF profile than the general population and lack the protective factors present in the control participants. Our results indicate that in the entire population, 24% of INPH may be explained by VRFs (PAR% of 24). This supports the hypothesis that VRF and VaDis contribute to the development of INPH, and that INPH may be a subtype of VaD. However, INPH is a heterogeneous syndrome. Normal senescence, disturbances in CSF dynamics, and other comorbidities are important in the development

Table 4 Obesity in patients with idiopathic normal pressure hydrocephalus (INPH) and the general population

Variable	Value or frequency (%) of each variable (no. of each variable/total no. of probands)			
	INPH	Controls	OR (95% CI)	p Value
Mean BMI	28.8 ± 5.2 SD (138)	26.6 ± 4.1 SD (325)	—	<0.001 ^a
Overweight or obese (BMI ≥ 25.0)	81.9 (113/138)	65.8 (214/325)	2.438 (1.487–3.995)	<0.001 ^b
Obese (BMI ≥ 30.0)	35.5 (49/138)	13.8 (45/325)	3.597 (2.233–5.794)	<0.001 ^b
Mean WTH ratio	0.978 ± 0.090 SD (140)	0.936 ± 0.096 SD (325)	—	<0.001 ^a
High WTH ratio (≥0.85 [female patients]; ≥0.90 [male patients])	91.4 (128/140)	72.6 (236/325)	5.698 (2.849–11.397)	<0.001 ^b

Abbreviations: BMI = body mass index; CI = confidence interval; OR = odds ratio; WTH = waist-to-hip ratio.

^aAnalysis of covariance: covariates: age and sex.

^bLogistic regression: ORs adjusted for age and sex.

of INPH.^{1-3,5,6} Nevertheless, a more aggressive approach in treating VRFs in patients with INPH is indicated.

Some researchers have hypothesized that VaDis may be a contributing cause of INPH.^{1,11-15} However, few studies have examined the association between VRFs and INPH. Existing studies have several limitations. These include small sample sizes,^{11,12,15} hospital-based controls,¹¹⁻¹³ or an imprecise diagnosis of INPH.^{12,15} Recently, the definitions of and treatments for VRFs have evolved. This implies that the results of studies examining VRFs in patients with INPH over 15 years ago^{11-13,15} may not be applicable today. The results of this study indicate that the independent VRFs in patients with INPH who have undergone shunting are hyperlipidemia, abdominal obesity, diabetes, and psychosocial factors. In addition, hypertension and physical inactivity were overrepresented in patients with INPH. These findings extend and confirm the findings of previous small VRF studies in patients with INPH¹¹⁻¹⁵ and correspond with VRF studies in other dementias. All of these VRFs are well-known risk factors for both Alzheimer disease and VaD.¹⁷

ApoB and ApoA1 are considered the best lipid profile measures and are better risk predictors for cardiovascular events.^{9,18} Low high-density lipoprotein cholesterol levels have been reported in patients with INPH.¹² However, the levels of apolipoproteins have not been studied previously in this population. In this study, patients with INPH had higher levels of disease-associated apolipoproteins than controls, based on all measures tested. This difference was not explained by a difference in the prescription of lipid-lowering drugs. These results indicate a strong association between INPH and hyperlipidemia. Manifest PVD and CVD were also overrepresented in patients with INPH. The strongest association was found for renal dysfunction; however, an association was also found for chronic kidney disease. Renal dysfunction and chronic kidney disease have not been described previously in INPH. Decreased renal function is a risk factor for both dementia and CVD, particularly cerebral small vessel disease (SVD).¹⁹ In addition, decreased renal function is associated with increased plasma concentrations of ApoB.²⁰

Our results suggest a strong association between INPH and abdominal obesity. High BMI has previously been reported to correlate with high lumbar CSF opening pressure.²¹ However, otherwise, obesity has rendered little interest in studies regarding INPH. Physical inactivity was also associated with INPH. Since gait disturbance is one of the cardinal

symptoms of INPH and physical inactivity is associated with obesity, the clinical relevance of this association is uncertain. However, abdominal obesity was associated with INPH even after adjusting for physical inactivity.

Psychosocial factors are some of the most important VRFs.^{9,10} In fact, this VRF had the second highest adjusted OR in this study. We have already shown that symptoms of depression are overrepresented in patients with INPH.⁸ A recent review identified psychosocial factors, mainly depression, as some of the most important modifiable VRFs for dementia prevention.¹⁷

In contrast with previous studies,^{3,11-14} our study indicates that hypertension is not independently associated with INPH. This does not necessarily mean that hypertension is not a VRF for INPH. Nowadays, there is a general high awareness of and improved treatment for hypertension. Approximately 60% of all participants were using antihypertensive treatments. In addition, the blood pressure measurements were obtained at 1 time point and do not indicate the longitudinal blood pressure in each individual. In contrast with previous studies,¹²⁻¹⁴ there was no association between cardiac disease and INPH. One explanation may be related to our exclusion of patients with severe dementia, who comprise a group with a presumably high frequency of cardiac disease. Furthermore, due to the risk of perioperative and postoperative complications, patients with severe coronary artery disease may not have been considered suitable for shunt surgery during the standard preoperative evaluation.

Comorbidity is an important predictor of the prognosis and long-time outcome of shunting in INPH.^{3,5,6,22} Vascular comorbidity may be associated with more severe symptoms and less postoperative improvement.⁵ However, most researchers agree that patients with extensive CVD should not be excluded from shunting.³⁻⁶ There are not many reports regarding the effects of coexisting VRFs on shunting.^{3,5} However, VRFs most often lead to VaDis. Most VRFs are treatable, either by lifestyle changes or by medication, recommended for the treatment of other dementias.¹⁷ Thus, we recommend that a thorough VRF analysis should be performed during the evaluation of patients with INPH, and that treatment for existing VRFs should be initiated.

INPH should be suspected when a patient presents with gait disturbances and VRFs. In a study examining hydrocephalic symptoms and ventriculomegaly in a population with CVD, 4% of the patients fulfilled the diagnostic criteria for possible INPH.²³ In a recent study, patients with Binswanger disease

benefitted from shunting.⁴ More studies on this subject are needed and a prospective trial of shunting on the basis of INPH symptoms, ventriculomegaly, and VRFs should be conducted. In addition, patients diagnosed with INPH should be compared to those diagnosed with VaD according to criteria such as those of the National Institute of Neurological Disorders and Stroke—Association Internationale pour la Recherche en l'Enseignement en Neurosciences. Considering the results in the present study together with repeated underdiagnosis and undertreatment of INPH,^{24,25} we suggest that when hydrocephalic symptoms and VRFs coexist with ventriculomegaly, the patient should be evaluated with tests specific for INPH (e.g., hydrodynamic testing, tap test, or extended lumbar drainage).

In agreement with previous studies, we found that CVD is overrepresented in INPH.^{1,3} Both subtypes of CVD are commonly seen in patients with INPH. The 2 types of CVD are SVD (e.g., white matter hyperintensities and lacunar infarctions) and large vessel disease (LVD) (e.g., stroke and TIA).^{3,23} Since LVD and SVD have different pathophysiologic pathways, they may contribute differently to INPH. The atherosclerosis of large vessels in LVD is well-described. In SVD, the roles of VRFs are not completely understood. In agreement with this study, other reports indicate that diabetes, hyperlipidemia, hypertension, and chronic kidney disease are risk factors.^{19,26} One hypothesis is that increased vascular stiffness with reduced dampening of arterial blood pressure and increased pulse pressure exposes the small vessels of the brain to increased wall stress.^{26,27} Endothelial failure and increased vascular permeability lead to chronic inflammation, damage to the blood–brain barrier, and an accumulation of toxic metabolites. At later stages, luminal narrowing and occlusion occur and precipitate ischemia, infarction, and impaired blood flow and metabolism in the deep white matter.^{26,27}

Increased CSF pulsation may be one of the pathophysiologic explanations for INPH.²⁸ Patients with INPH exhibit characteristics similar to those of patients with SVD. These characteristics include reduced periventricular metabolism, reduced cerebral blood flow in the periventricular and frontal subcortical areas of the brain, lacunar infarctions, and microbleeds.^{3,29–31} Biomarkers of axonal damage and chronic ischemia have also been found in the CSF of patients with INPH.^{3,16,29} Thus, we suggest that SVD and its VRFs in combination with increased CSF pulsations may be important parts of a pathophysiologic pathway in INPH. If the stiffening of central arteries causes a chronic increase in cerebral arterial pulsatility, which

indirectly increases CSF pulsations, a lowering of intracranial pressure with shunting would increase intracranial compliance and potentially normalize the pulsations. In addition, the alternate route for CSF outflow that a shunt provides could, hypothetically, moderate the vicious cycle of SVD by facilitating the transportation of toxic metabolites, leading to reduced inflammation and probably increased cerebral blood flow and increased metabolism. More studies are needed.

The strengths of this study include large samples of representative cases and controls, a proper diagnosis of INPH, and population-based controls without selection bias. These factors should lead to high generalizability for our study. In order to minimize bias in collecting data and to increase internal validity, all data were assessed in the same standardized manner for all participants. One limitation of our study was the exclusion of patients with MMSE scores <23, which may have increased the risk of a type 2 error. This rather strengthens the associations between the VRFs and INPH. However, some of the associations may have been stronger if the patients with the lower MMSE scores were included. Another limitation was that the VRFs were assessed postoperatively and that the VRF profiles of patients with suspected INPH who did not undergo shunting are unknown. Thus, this study does not prove causality. Theoretically, the VRFs may not have existed before the surgery. However, there is little reason to believe this. VRFs and subsequent VaDis develop over a long period and there was no difference in VRFs between patients with INPH from the 3 different years of surgery. The results of this study confirm and extend the findings of previous risk factor studies conducted before shunting.^{11–15} There are several plausible pathophysiologic explanatory models for VRFs acting as risk factors for INPH. However, there are no models suggesting INPH as a risk factor for VaDis. Other limitations include the fact that CVD was self-reported and that even though the calculated PAR% was 24, the potential for prevention could not be proved using our data.

Patients with INPH have higher rates of VRFs and VaDis than the general population. Hyperlipidemia, abdominal obesity, diabetes, and psychosocial factors are associated with INPH independently of age, sex, and other VRFs. In addition, hypertension, CVD, and PVD are overrepresented in INPH. In the entire population, 24% of cases of INPH may be explained by VRFs. This suggests that INPH may be a subtype of VaD. SVD may have an important role in the pathophysiology of INPH. A VRF analysis should be undertaken in the preoperative evaluation of each

patient with INPH and treatment for existing VRFs should probably be initiated, whether the patient is selected to undergo shunting or not.

AUTHOR CONTRIBUTIONS

All authors approved the submitted manuscript and agree to be accountable for all aspects of the study. All authors made substantive intellectual contributions to the submitted manuscript, as follows: Hanna Israelsson substantially contributed to the conception of the study, designed the study, collected, analyzed, and interpreted the data, wrote the first draft, and completed the manuscript. Bo Carlberg substantially contributed to the design of the study and interpretation of the data and critically revised the work for important intellectual content. Carsten Wikkelsö, Katarina Laurell, Babar Kahlon, and Göran Leijon substantially contributed to the acquisition of the participants and critically revised the work for important intellectual content. Anders Eklund supervised the study, substantially contributed to the design of the study and the analysis and interpretation of the data, and critically revised the work for important intellectual content. Jan Malm supervised the study, substantially contributed to the conception and design of the study and the analysis and interpretation of the data, and critically revised the work for important intellectual content.

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DISCLOSURE

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

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