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The prevalence of cardiovascular disease in non-communicating hydrocephalus

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ABSTRACT

Objective: Hydrocephalus (HC) caused by blockade of ventricular cerebrospinal fluid (CSF) pathways is denoted non-communicating HC. One issue not previously addressed is how the prevalence of cardiovascular disease compares between patients with non-communicating HC and the general population.
Methods: We examined whether the prevalence of cardiovascular disease (arterial hypertension, angina pectoris, cardiac infarction, and diabetes) differed between cases with non-communicating HC and a general control population, represented by participants of the North-Trøndelag Health 3 Survey (The HUNT3 Survey). A second control group consisted of patients with communicating hydrocephalus (idiopathic normal pressure hydrocephalus, iNPH).
Results: The study included 50 cases with non-communicating HC (53.4 + 10.5 years), and two control cohorts: 35,413 participants of the HUNT3 Survey (52.8 + 9.6 years), and 176 iNPH patients (61.2 + 8.3 years). All individuals were aged 35–70 years. Among the non-communicating HC patients, the results showed increased prevalence for arterial hypertension (males), cardiac infarction (females), and diabetes (females), as compared with the HUNT3 control group with significant odds ratio estimates. However, the prevalence of cardiovascular disease did not significantly differ between patients with non-communicating HC or iNPH. In patients with either non-communicating HC or iNPH and elevated pulsatile intracranial pressure (ICP) during overnight monitoring, the prevalence of diabetes was increased.
Conclusion: This study showed significantly increased prevalence of cardiovascular disease in non-communicating HC, indicating an association between cardiovascular disease and the development of non-communicating HC. Further, diabetes was associated with abnormal pulsatile ICP in both non-communicating HC and iNPH patients.

1. Introduction

Hydrocephalus (HC) was differentiated into the subtypes *non-communicating* and *communicating* HC about 100 years ago by Dandy and Blackfan [1]. In the non-communicating type, the location of cerebrospinal fluid (CSF) flow obstruction is assumed to be within the ventricular CSF pathways, for example in the aqueduct of Sylvius. However, the pathophysiology of non-communicating HC remains poorly understood. Hence, despite evidence of CSF obstruction, some patients do not develop HC, and overnight intracranial pressure (ICP) monitoring may reveal normal pulsatile and static ICP scores, indicating that CSF obstruction not always is accompanied with intracranial hypertension [2]. In line with these observations, we found no significant association between the ventricular volume and the pulsatile/static ICP scores in patients with non-communicating HC [3]. Furthermore, even though CSF obstruction is considered the cause of non-communicating HC, it has presently not been established whether endoscopic third ventriculostomy (ETV) is superior to shunt surgery in non-communicating HC [4]. Taken together, several lines of evidence suggest that other factors than CSF obstruction *per se* are required for the development of non-communicating HC.

Recently the glymphatic system was discovered in rodents [5], which is a transparenchymal and paravascular pathway for exchange of CSF and interstitial fluid (ISF) and clearance of waste solutes from the brain. The rate of paravascular CSF-ISF exchange became impaired when the arterial pulsatility was reduced [6], and also became reduced with increasing age [7]. Hence, the par-

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avascular route for exchange of CSF/ISF and waste solutes seems to be highly dependent on the function of the cerebrovascular system. It is reasonable to speculate that altered function of the cerebrovascular system may play a key role regarding the pathophysiology of both communicating and non-communicating HC. In a communicating type of HC denoted idiopathic normal pressure hydrocephalus (iNPH), the prevalence of cardiovascular disease was significantly increased, suggesting that cardiovascular disease is involved as an exposure in the development of iNPH [8]. We hypothesized that cardiovascular disease is involved as an exposure also in the development of non-communicating HC.

On this background, we explored whether the prevalence of cardiovascular disease is increased in non-communicating HC. Two different control cohorts were included, namely the participants of the Nord-Trøndelag Health 3 Survey (The HUNT3 Survey), which represents the general control population. The second control cohort consisted of patients with iNPH, which represents another HC population.

2. Methods

2.1. Patient material

The study was approved by The Regional Committee for Medical and Health Research Ethics (REK) of Health Region South-East, Norway (2012/1180), and by Oslo University Hospital (2011/6692), Oslo, Norway.

2.1.1. Non-communicating HC

The patient material included all patients aged 35–70 years with non-communicating HC due to stenosis of the aqueduct of Sylvius managed within the Department of neurosurgery, Oslo University Hospital-Rikshospitalet, during the 10-year period 2002–2011. The diagnosis of non-communicating HC was based on magnetic resonance imaging (MRI) demonstrating stenosis of the aqueduct of Sylvius.

2.1.2. Population based HUNT3 cohort

In order to estimate the prevalence of cardiovascular disease in a control population, we used data from The HUNT3 Survey. During the period 2006–2008, all inhabitants in the county of Nord-Trøndelag, Norway, aged 20 years and older were invited to participate in a general health study, named *Nord-Trøndelag Health Study* 3 (The HUNT3 Survey; http://www.ntnu.no/hunt). This study included questionnaires about cardiovascular disease. The population of Nord-Trøndelag County is stable and homogenous with less than 3% non-Caucasians, and is representative for Norway in general, though not containing any large cities. Individuals aged 35–70 years were included in the analysis.

2.1.3. iNPH patients

The second control material included patients managed for iNPH within the Department of neurosurgery, Oslo University Hospital-Rikshospitalet, during 10-year period 2002–2011. Only patients aged 35–70 years of age were included. As previously described [8], the diagnosis of iNPH was based on clinical neurological examination, radiological assessment of ventricular size using computed tomography (CT) or MRI.

To allow for reliable comparisons between cases and controls, all individuals were aged 35–70 years.

2.2. Identification of cardiovascular disease as a risk factor

The identification of cardiovascular disease was defined in the same way in the non-communicating HC cases, and the HUNT3 and iNPH control cohorts. With regard to the non-communicating HC (i.e. cases) and iNPH (i.e. controls) patients, cardiovascular disease was reported by the referring doctor/neurologist, and/or by the patient or his/her relatives. In The HUNT3 Survey (i.e. controls), the participants self-reported cardiovascular disease in a standardized questionnaire. The following questions were answered by the patients/relatives:

- Do you take or have you taken medication for high blood pressure?
- Have you had or do you have any of the following: angina pectoris (chest pain)?
- Have you had or do you have any of the following: myocardial infarction (heart attack)?
- Have you had or do you have any of the following: diabetes?

2.3. Prevalence of cardiovascular disease versus pulsatile intracranial pressure

All non-communicating HC and iNPH patients had undergone over-night monitoring of pulsatile ICP, as previously described [9]. The patients were dichotomized according to thresholds of pulsatile ICP, i.e. mean ICP wave amplitude (MWA) >4 mmHg on average during over-night monitoring and >5 mmHg during >10% of recording time [9]. The occurrence of cardiovascular disease in patients with MWA either below or above thresholds was determined.

2.4. Statistical analysis

Statistical analyses were performed using the SPSS software version 22 (IBM Corporation, Armonk, NY). Descriptive statistics are mean (standard deviation) or number of patients (percentage). Difference between groups was assessed with student t-test or chi-

Table 1
Demographic data of case (ncHC) and control (HUNT-3/iNPH) cohorts, all aged 35–70 years.

	Case cohort	Control cohorts			
	[a]ncHC	[b]HUNT3	*p*-value (ncHC vs HUNT3)	[c]iNPH	*p*-value (ncHC vs iNPH)
N	50	35,413		176	
Gender (F/M)	24/26	18,988/16,425	0.43	95/81	0.46
Mean age (±std)	53.4 ± 10.5	52.8 ± 9.6	0.67	61.2 ± 8.3	<0.001
Arterial hypertension (N/%)	16 (32%)	6493 (18.3%)	0.01	72 (40.9%)	0.25
Angina pectoris (N/%)	2 (4%)	726 (2.1%)	0.33	16 (9.1%)	0.24
Cardiac infarction (N/%)	4 (8%)	747 (2.1%)	0.004	15 (8.5%)	0.91
Diabetes mellitus (N/%)	6 (12%)	1404 (4.0%)	0.004	26 (14.8%)	0.62

[a] ncHC = non-communicating hydrocephalus.
[b] HUNT3 = The HUNT3 Survey.
[c] iNPH = idiopathic normal pressure hydrocephalus. Assessment of statistical significance: Independent samples t-test for continuous data and Pearson Chi-square test for categorical data.