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Familial aggregation of idiopathic normal pressure hydrocephalus: Novel familial case and a family study of the NPH triad in an iNPH patient cohort

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ABSTRACT

Objective: Idiopathic normal pressure hydrocephalus (iNPH) is considered sporadic, yet familial cases involving single pedigrees are being increasingly recognized. As current evidence does not extend beyond isolated pedigrees, we aimed to determine the putative heritability of iNPH by examining the prevalence of the iNPH triad among the family members of iNPH probands.

Method: We present a case–control family study of the iNPH symptom triad among the relatives of iNPH patients (n = 20) identified from a cohort of patients undergoing CSF diversion and matched comparison subjects (n = 21). A total of 291 first-degree relatives from 41 families were characterized using semi-structured family history interviews. Independent from the family study, we present a novel well-characterized familial case of iNPH.

Results: ≥2 insidious, progressive and idiopathic iNPH symptoms were identified among first degree relatives in 6 iNPH pedigrees (2 multiply affected) and 1 control pedigree, with an incidence of 7.1% among iNPH relatives and 0.7% among control relatives (OR = 11.53). Gait disturbance and memory impairment began at a younger age among the relatives of iNPH probands. Independent of our family study, we present a novel case report of a large iNPH pedigree with multiple affected relatives.

Interpretation: Our family study and novel familial case suggest familial aggregation of iNPH. A larger family study with full characterization of affected and unaffected relatives is warranted. Confirmation of heritability may allow identification of individuals at high-risk for iNPH, early intervention, and improved aetiological elucidation.

1. Introduction

1.1. Background

Normal Pressure Hydrocephalus (NPH) is a syndrome described as a triad of gait unsteadiness, urinary incontinence and memory impairment in the context of ventriculomegaly and normal cerebrospinal fluid (CSF) pressure [1]. In the absence of precipitants including traumatic brain injury, subarachnoid hemmorhage or meningitis, the syndrome is termed idiopathic NPH (iNPH).

Although iNPH is considered sporadic, to our knowledge a formal test of heritability or familial aggregation is absent from the literature. In light of a growing number of familial case reports [2–7], we believe the current state of evidence in iNPH behooves the clinician and researcher alike to revisit this potentially errant assumption. Clearly, this may be clinically deleterious to patients by delaying recognition of the syndrome. Further, forgoing the potential recognition of a genetic basis for iNPH might preclude an opportunity to improve aetiological understanding and develop novel interventions.

Yet, a literature wherein familial aggregation is reported in single pedigrees, by itself, does not warrant an extensive, potentially invasive, and costly characterization of relatives. To provide a characterization of the putative familial aggregation of iNPH, we first aimed to perform a family study of iNPH symptomatology in a cohort of patients diagnosed with iNPH undergoing CSF diversion surgery. Specifically, we characterized the familial presence of the iNPH symptom triad that was insidious, progressive, and idiopathic among the relatives of iNPH probands and the relatives of control probands. Though not a conclusive method of diagnosing iNPH, this validated method of retrospectively assessing the risk of a diagnosis of iNPH [8] was selected as a preliminary test of iNPH heritability.

Finally, we present a novel case of familial iNPH independent of the family study, with detailed characterization of relatives within a large pedigree in which four relatives, three of whom underwent successful CSF diversion surgery, presented with iNPH.

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2. Methods

2.1. iNPH probands

We identified 690 patients having undergone ventriculoperitoneal (VP) CSF diversion at St-Michael's Hospital from 2004–2010. From this list, 52 patients had a pre-operative diagnosis of iNPH.

One case previously identified and reported on as familial [2] was excluded.

An invitation letter was sent and followed-up by telephone. Of the initial cases, fourteen cases could not be recruited due to death (n = 9) or invalid contact information (n = 5). Of the remainder, 21 (56.7%) patients returned the study questionnaire package. One participant's contact information changed mid-study, and did not complete the family interview.

Two patients (10%) were reported on entirely by informants (a first degree relative).

2.2. Control probands

We attempted to identify control probands using the acquaintanceship method [9]. Using this method, NPH probands are asked to name a family friend (non-relative) of similar age and sex to serve as a control. This method minimizes differences in sex, age, ethnicity, marital status, socioeconomic status, education and family density. Ten NPH cases identified controls using this approach. For the remainder, control participants were identified among neurosurgical patients seen at St-Michael's Hospital (acoustic neuroma 14 years post-resection n = 1, glioma n = 1, spinal pathology n = 9).

2.3. Assessment

In addition to the 2 iNPH probands for whom demographic and head injury information was provided by a first degree relative, an additional 7 (35%; total 45%) of iNPH proabnds elected to have an informant undergo the semi-structured family interview in collaboration or in their stead. The principal reason cited by probands for involving an informant (in all cases a first degree relative) was geographic distance from family resulting in incomplete information. Comparison subjects also provided contact information for a relative to complete family history information in 4 cases (19%). This reflects an attempt by design, and participant willingness, to obtain complete and accurate family history information.

For each proband, pedigrees were constructed prior to performing a semi-structured family history interview. To maximize quality of information, we focused on first degree relatives. A total of 291 first degree relatives were characterized, 140 of whom were related to iNPH probands and 151 to control probands. No age difference was observed (62.64 ± 19.28 vs. 60.20 ± 19.28, $p = .292$). A comparable proportion of relatives were deceased (39.3% vs. 37.1%).

Miscarriage and Down syndrome were characterized as a proxy for chromosomal abnormalities. Other relevant conditions, including Spina Bifida, epilepsy, Alzheimer's disease, Parkinson's disease, hypertension, cerebrovascular accident, myocardial infarction, diabetes mellitus, multiple sclerosis, rheumatological conditions, and psychiatric conditions were characterized.

The iNPH triad, namely difficulties observed or expressed by caregivers with respect to urinary continence, gait instability or memory, were further explored and considered present only if they were 1) insidiously progressive, 2) were not attributable to cerebrovascular incident, chronic illness, malignancy or trauma, 3) not reversible by focally directed treatment such has joint replacement, spinal surgery, or urological surgery, and 4) the symptoms had not been investigated and more appropriately diagnosed.

Lifetime history of head trauma was assessed using the Traumatic Brain Injury Questionnaire – Community Version (TBI) [10]. The instrument explores head trauma including the context of injury, the mechanism, treatment, and loss of consciousness.

2.4. Validity of iNPH proband data

In addition to complementing family history information with an informant, we sought further to ensure the validity of iNPH probands' data. Therefore, for a subset of iNPH probands (n = 11), demographic, past medical history and history of head trauma was provided by both the proband and an informant. Informants included sibling, child and spouse.

Perfect concordance was observed between probands and informants for demographic and past medical history. Moderate consistency between probands and informants was noted when considering the presence or absence of head trauma ($\kappa = .600$), with informants under reporting incidents. Nevertheless, excellent consistency ($\kappa = 1.00$) and symmetry ($\gamma = 1.00$) was noted when considering vehicle crashes.

2.5. Statistical analyses

We performed analyses using the SPSS statistical package version 19 (SPSS Inc., Chicago, IL). Data distributions were checked for normality. Chi square tests were used for categorical measures, student t-test was used for continuous variables. Logistic regression with

Table 1
Demographic characteristics and past medical history.

	NPH (N = 20)	Control (N = 21)		
	% or M ± SD	% or M ± SD	$\chi 2$	p
Age (years)	73.85 ± 7.40	71.24 ± 7.55	t(39) = 1.11	.271
Sex			.26	.606
Male	7 (35.0%)	9 (42.9%)		
Female	13 (65.0%)	12 (57.1%)		
Ethnicity			.176	.675
Caucasian	19 (95.0%)	18 (85.7%)		
Other	1 (5.0%)	3 (14.3%)		
Civil status			2.30	.680
Married	12 (60.0%)	13 (61.9%)		
Divorced/separated	4 (20.0%)	4 (19.0%)		
Widowed	4 (20.0%)	3 (14.3%)		
Single	0 (0.0%)	1 (4.8%)		
Lives alone	8 (40.0%)	8 (38.1%)	.01	.901
Education			8.89	.351
High school incomplete	5 (25.0%)	5 (23.8%)		
High school complete	3 (15.0%)	4 (19.0%)		
Technical degree	2 (10.0%)	3 (14.3%)		
University	9 (45.0%)	6 (28.6%)		
Professional degree	1 (5.0%)	0 (0.0%)		
Post-graduate degree	0 (0.0%)	3 (14.3%)		
Annual household revenue			6.29	.505
<$20,000	2 (10.0%)	3 (14.3%)		
$20,001–$40,000	4 (20.0%)	7 (33.3%)		
$40,001–$60,000	4 (20.0%)	1 (4.8%)		
$60,001–$80,000	5 (25.0%)	3 (14.3%)		
$80,001–$100,000	1 (5.0%)	3 (14.3%)		
>$100,000	3 (14.3%)	3 (15.0%)		
Past medical history				
Hypertension	12 (57.1%)	16 (69.6%)	.73	.392
Diabetes mellitus	5 (23.8%)	1 (4.3%)	3.53	.060
Emphysema	2 (9.5%)	1 (4.3%)	.46	.496
Epilepsy	0 (0.0%)	1 (4.3%)	.93	.334
Myocardial infarction	1 (4.8%)	2 (8.7%)	.26	.605
Congestive heart failure	0 (0.0%)	1 (4.3%)	.93	.334
Stroke	0 (0.0%)	2 (8.7%)	2.94	.230
Hypothyroidism	3 (14.3%)	3 (13.0%)	.01	.905