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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

main effects and interactions were also employed. Significance was set at $\alpha < 0.05$.

3. Results

Sociodemographic information and past medical history is provided in Table 1. No differences were noted between iNPH and control probands. A trend was noted with respect to increased prevalence of diabetes mellitus among iNPH probands.

Loading of symptoms of the iNPH triad is presented in Fig. 1. Significant overlap between symptoms was noted among iNPH relatives, and disparate iNPH symptoms were observed among control relatives. Concurrence of ≥2 iNPH symptoms was greater for all combinations including the full iNPH triad. The number of iNPH relatives exhibiting ≥2 iNPH symptoms was higher than control relatives (n = 10,7.1% vs. n = 1,0.7%; $\chi 2 = 8.38$, $p \leq .01$). Two or more iNPH symptoms were noted among at least one first degree relative of 6 iNPH and 1 control pedigrees (30%vs4.8%, $\chi 2 = 4.60$, $p \leq .05$). Two iNPH pedigrees and no control pedigrees demonstrated multiple affected first degree relatives (Fig. 2A–B).

iNPH relatives exhibited gait abnormalities (77.21 ± 11.25vs.86.17 ± 10.72 years, M-W = 26.50, p = .050) and memory impairment (76.88 ± 7.99vs.82.50 ± 13.80 years, M–W = 32.00, $p \leq .05$) at an earlier age than control relatives. No difference was noted with respect to urinary incontinence (74.38 ± 12.46vs.76.50 ± 9.44 years).

With respect to family history of other conditions (Supplementary Table 1), iNPH relatives were significantly less likely to have diabetes mellitus ($\chi 2 = 4.39$, $p \leq .05$; OR = .342, 95%CI: .188 to .963) or hypertension ($\chi 2 = 9.82$, $p \leq .01$; OR = .37, 95%CI: .196 to .700).

Blunt head injury was reported by significantly more iNPH probands than control probands (n = 16, 72.7% vs. n = 8, 28.1%, $\chi 2 = 5.22$, $p \leq .05$; OR = 4.33, 95%CI: 1.19 to 15.69). This was most notably the case with respect to vehicle crashes (.54 ± 1.01 vs. .04 ± .21, $p \leq .05$), particularly car crashes (.40 ± .79 vs. .04 ± .21, p = .05) but significant bicycle (n = 1) and plane crashes (n = 1) were also reported by iNPH probands. A binary logistic regression predicting proband status failed to demonstrate a significant interaction between familial aggregation and head injury above and beyond the main effects of these variables (p = .999).

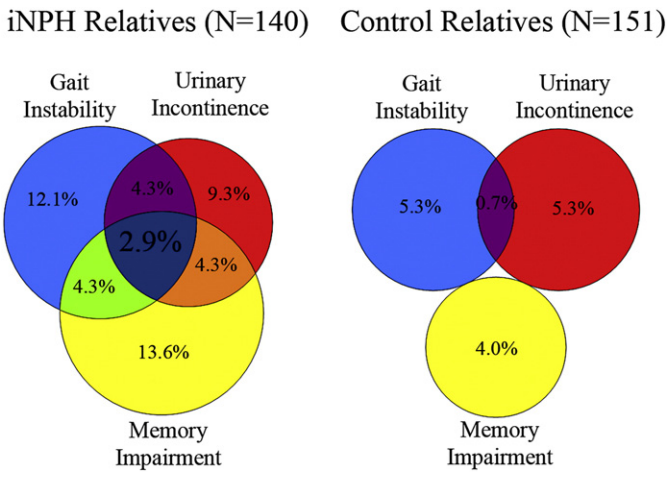

Fig. 1. Familial loading of iNPH symptoms among first degree relatives of 20 iNPH probands and 21 comparison probands. Gait instability and urinary incontinence: n = 6 (4.3%) vs. n = 1 (0.7%), $\chi 2 = 4.06$, $p \leq .05$. Gait instability and memory impairment: n = 6 (4.3%) vs. n = 0 (0.0%), Fisher's Exact $p \leq .05$. Memory impairment and urinary incontinence: n = 6 (4.3%) vs. n = 0 (0.0%), Fisher's Exact $p \leq .05$. Full iNPH symptom triad: n = 4 (2.9%) vs. n = 0 (0.0%), Fisher's Exact p = .05.

4. Case report

4.1. Proband

4.1.1. History

The proband was a 67 year old, right hand dominant, married, a mother of 3, and a retired social worker. Her chief complaint was of worsening gait instability. This had been insidiously worsening over the previous 6 years, to the point where did not confidently cross streets for fear of taking too long. She also endorsed a history of worsening urinary stress incontinence that began 1 year after her gait instability was noted. With respect to her cognitive function, the proband reported increasing difficulty keeping her notes organized, misplacing items, and difficulty articulating her thoughts. She denied a history of meningitis or subarachnoid hemorrhage. No history of significant head trauma could be elicited, yet she did report a bookshelf falling on her head three years prior without loss of consciousness, amenesia, or symptoms of concussion.

The proband's medical history included hypertrophic cardiomyopathy, diabetes mellitus, hypothyroidism, depression, nystagmus, ovarian cyst, cataract surgery in the left eye and bilateral tonsillectomy. Her medications included atenolol, atorvastatin, metformin, levothyroxine, tolterodine and bupropion. She quit smoking 48 years prior to presentation and was social drinker (1–2 standard drinks per week). She had no known drug allergies.

4.1.2. On examination

On examination, she was quiet and expressionless. She was alert and oriented to self and place, but named the incorrect year. She displayed evidence of postural instability. Her gait revealed significantly reduced stride length, requiring 32 steps and 19.9 seconds to complete a 10-meter walk test. Her Folstein exam revealed a score of 26/30 (−1 orientation, −3 delayed recall). Her cranial nerves were normal with the exception of bilateral end gaze nystagmus and mild left optic atrophy on fundoscopy. Her motor exam revealed normal bulk, tone and power, symmetrical 2+ reflexes, negative Hoffman's sign, no clonus and downgoing toes. We noted a tremor and cogwheeling in both arms. She had intact sensation with respect to light touch, temperature, pain, proprioception, with some decreased vibration sense in a glove and stocking distribution. Cerebellar testing revealed no abnormalities.

4.1.3. Pre-operative investigations

Her blood work revealed a normal complete blood count in addition to normal levels of vitamin B12, folate and thyroid stimulating hormone.

A lumbar drain, with an opening pressure within normal limits, was inserted and 230 ml of CSF was drained over 3 days, resulting in transient improvement in her gait which returned to baseline after 48 h.

CSF analysis revealed no abnormalities.

A structural MR of the brain (Fig. 3A) revealed enlargement of the lateral, third and fourth ventricles, a flow void in the cerebral aqueduct, but no transependymal flow. The interfrontal distance was 4.6 cm and the inner table distance was 10.7 cm (Evans index = 0.42).

A radionucleotide cisternogram revealed rapid ascent and persistence of the tracer at 48 h.

4.1.4. Response to CSF diversion

The proband underwent ventriculoperitoneal shunt placement (Fig. 4A) with a programmable shunt initially set at the equivalent of a medium pressure setting (Medtronic Strata setting 1.5).

Post-operatively she experienced significant improvement in her gait and reduced number of episodes of urinary stress incontinence, which was confirmed by her husband. No observable change in cognitive function was noted (identical Folstein). Her gait was significantly

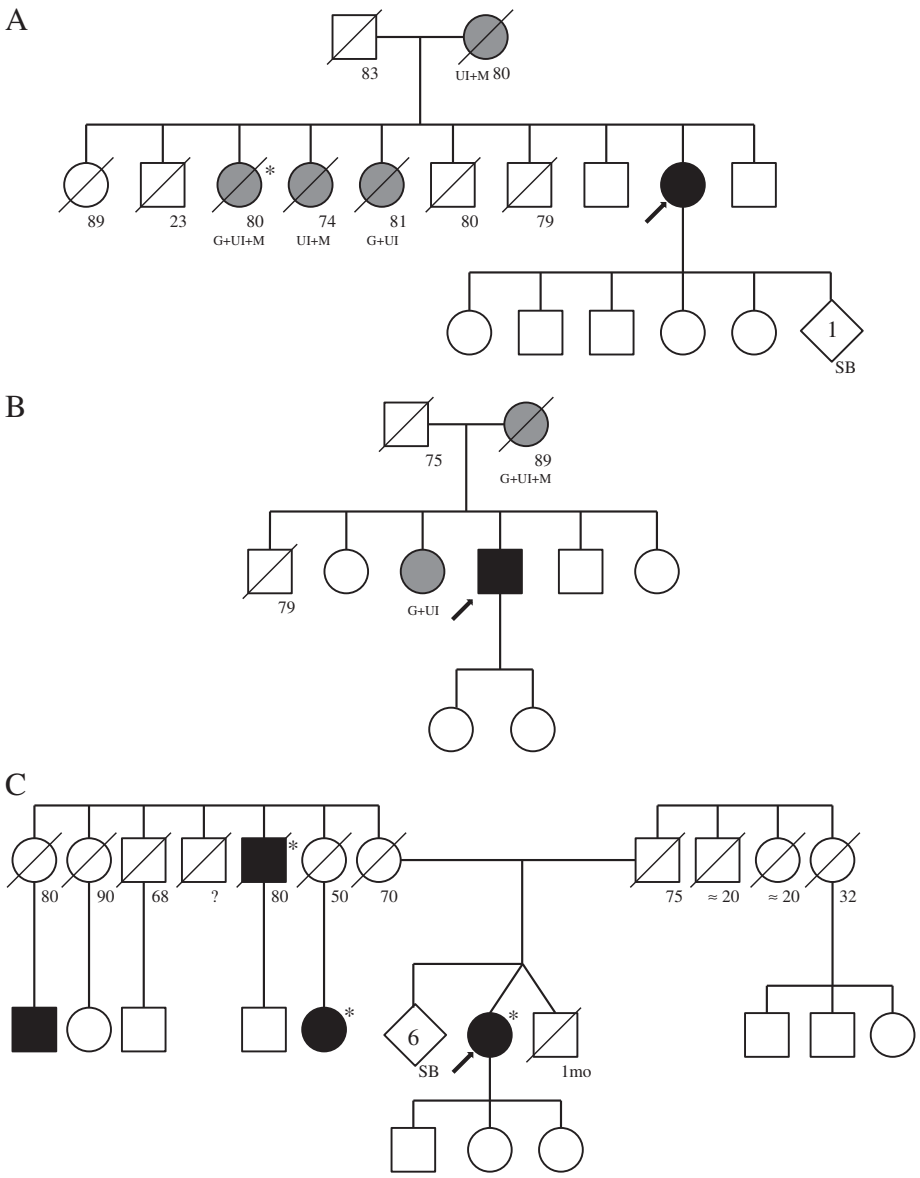

Fig. 2. A–B) Family pedigree of first degree relatives for family-study families with multiple relatives with possible iNPH. C) Family pedigree of first and second degree relatives of the case proband. Grandparents are not presented as the quality of information was poor. * = CSF diversion; SB = Still Birth; Black = Diagnosed iNPH; Grey = endorsing ≥2 iNPH symptoms. A) The proband's mother was noted to have memory symptoms beginning at approximately 50 years of age and was incontinent of urine at approximately 60 years of age. The proband's eldest affected sister was noted to have symptoms of gait instability and memory disturbance at approximately 60 years of age, with the family having knowledge of urinary incontinence at approximately 70 years of age. The proband's middle affected sister was reported to have voiced incontinence symptoms as of 55 years of age, with memory symptoms beginning at 60 years of age. The proband's youngest affected sister was noted to have an unstable gait and urinary incontinence beginning at approximately 70 years of age. B) The proband's mother developed symptoms of a broad-based unstable gait and memory impairment at approximately 75 years of age. The family reports knowledge of complete urinary incontinence at approximately 80 years of age. The proband's brother was known to have 'low IQ' early in life and was noted to develop an unstable gait and urinary incontinence in his 70s. C) Case report pedigree.

improved, with a 10-meter walk test requiring only 21 steps and 15 s (compared to 32 and 19.9 s pre-operatively).

Post-operative computed tomography imaging revealed appropriate shunt position and did not reveal interval change in the proband's ventriculomegaly.

4.1.5. Follow-up

The proband has been followed for 55 months post-operatively and has continued to demonstrate sustained improvement in his gait and urinary incontinence. She unfortunately has not improved with respect to her cognitive status, and continued to be unable to perform delayed recall and had some difficulty with respect to orientation to time.

5. Relative

5.1. History

The relative was a maternal cousin of the proband.

She was a 67 year old, right hand dominant woman, widowed, mother of 2. Her chief complaint was balance and walking difficulties. This problem had been progressively worsening over the last four years, with at least two documented falls, and concomittant development of urinary incontinence. Her family members reported that she was becoming increasingly confused and had been having difficulty with her memory for the last year. At presentation, she could no longer walk and required two-person assistance for transfers. Her family denied a history of meningitis, subarachnoid hemorrhage or head trauma.

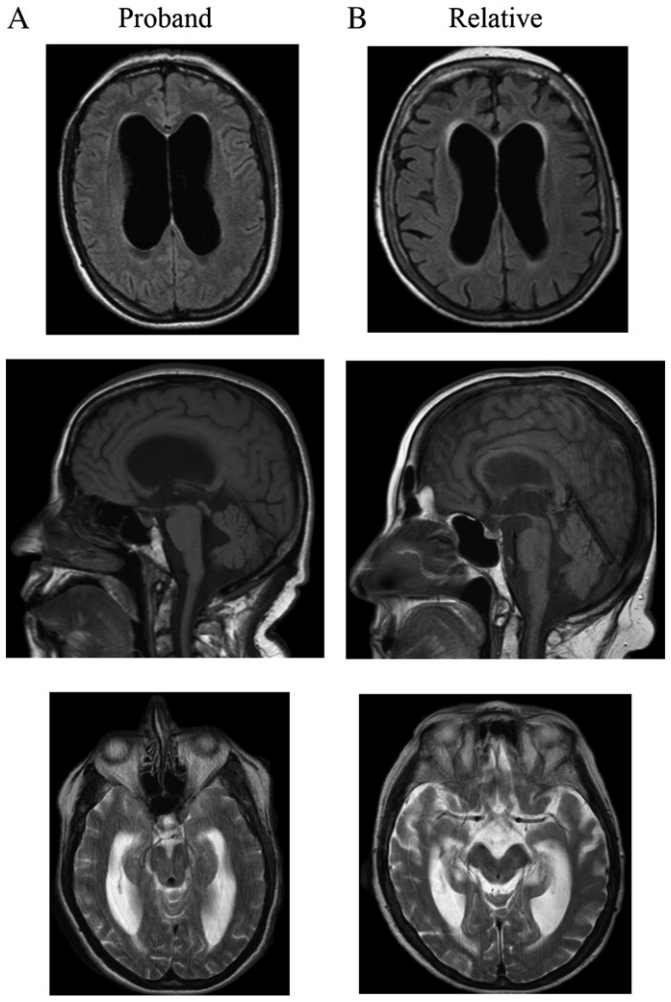

Fig. 3. Case report pre-operative imaging. A) Proband MRI demonstrating communicating ventriculomegaly with a flow void in the cerebral aqueduct. B) Relative MRI demonstrating communicating ventriculomegaly with a flow void in the cerebral aqueduct.

The relative's past medical history includes arthritis, chronic renal failure, hypertension, hypothyroidism, osteoporosis and bipolar affective disorder. She had never had surgery. Her medications included acetylsalicylic acid, furosemide, amlodipine, levothyroxine, risedronate, divalproic acid, and galantamine. She had a ten pack year history of smoking, having quit 15 years prior. She rarely consumed alcohol. She was allergic to codeine and contrast dye.

5.2. On examination

On examination, she was noted to be expressionless, communicated with great difficulty, and was not moving her limbs. She was oriented to self and place, but was mistaken with respect to the year. She required two people assisting in order to rise and remain upright, and exhibited great difficulty walking with a magnetic gait and significant reduction in stride length. She displayed evidence of significant postural instability with retropulsion. She was uncooperative with cognitive testing, however a MOCA score of 8/30 was documented from a previous medical admission. Her cranial nerves were normal. Her motor exam revealed generalized weakness, symmetrical 1+ reflexes, negative Hoffman's sign, no clonus and downgoing toes. A positional tremor was observed bilaterally that was worse on the left. She had intact sensation with respect to light touch, temperature, pain, and proprioception. Cerebellar testing revealed dysmetria on finger to nose testing.

5.3. Pre-operative investigations

On initial consultation, the patient's blood work initially revealed elevated creatinine (396 umol/L; 42-102umol/L), neutrophilia (19.47× 10*9; 4–11×10*9) and an elevated thyroid stimulating hormone (10.83 mU/L; 0.40–5.50 mU/L). 14 weeks after appropriate management, her gait, urinary incontinence and memory had continued to decline.

CSF analysis revealed lower limit of normal level of protein, and no other abnormalities.

A structural MR of the brain (Fig. 3B) revealed widened Sylvian fissures, enlarged lateral, third, and fourth ventricles as well as a flow void in the aqueduct. There was minimal transependymal flow. The interfrontal distance was 6.1 cm and the inner table distance was 13.3 cm (Evans index = 0.46).

A single photon emission computed tomography and perfusion MR of the brain were performed, demonstrating a pattern consistent with Alzheimer's with ventriculomegaly.

Due to lumbar stenosis, the patient had a fluoroscopic guided radionucleotide cisternogram, revealing rapid ascent and persistence of the tracer in the ventricles at 48 hours.

5.4. Response to CSF diversion

The relative underwent ventriculoperitoneal shunt placement (Fig. 4B) with a programmable shunt initially set at the equivalent of a medium pressure setting (Medtronic Strata setting 1.5).

Post-operatively her family members reported that they saw marked improvements in her alertness and memory. On assessment, she was spontaneously moving all limbs, was communicative whereas she had previously been quasi-quadriparetic and non-communicative. This, however, appeared to unmask behavioural issues, most notably anger, and as such cognitive assessment was not possible. With respect to gait, she demonstrated significant improvement with respect to fluidity and length, yet remained very unstable and still required assistance.

6. Family history

The family pedigree is presented in Fig. 2C. The pedigree was constructed with the proband and confirmed by the proband's and the relative's family members. On the paternal side, all but the proband's father died at a very young age during the Second World War.

In addition to the proband and relative described, several of the proband's maternal relatives were diagnosed and treated for iNPH. One uncle was diagnosed with iNPH and underwent CSF diversion surgery. Prior to surgery, the man was wheelchair bound, incontinent of urine and confused. After surgery, he was ambulating independently. A second relative, a cousin, was diagnosed with NPH but has elected not to undergo CSF diversion surgery.

7. Discussion

iNPH is an increasingly recognized cause of disability and though iNPH is considered rare, a large neuroimaging characterization of individuals from the general Japanese community suggests that this condition may affect as many as 1.5% of individuals over the age of 65 [11]. Currently, surgical treatment is available for this syndrome involving the diversion of CSF that results in symptom improvement for a significant number of patients [12,13]. By recognizing individuals at high-risk for the development of iNPH, earlier identification and more timely surgical intervention may become possible in order to better preserve function. Moreover, by studying those at high risk, our understanding of the natural history of this syndrome may be improved, which, in turn, may lead to novel or prophylactic intervention in order to further improve clinical outcomes.

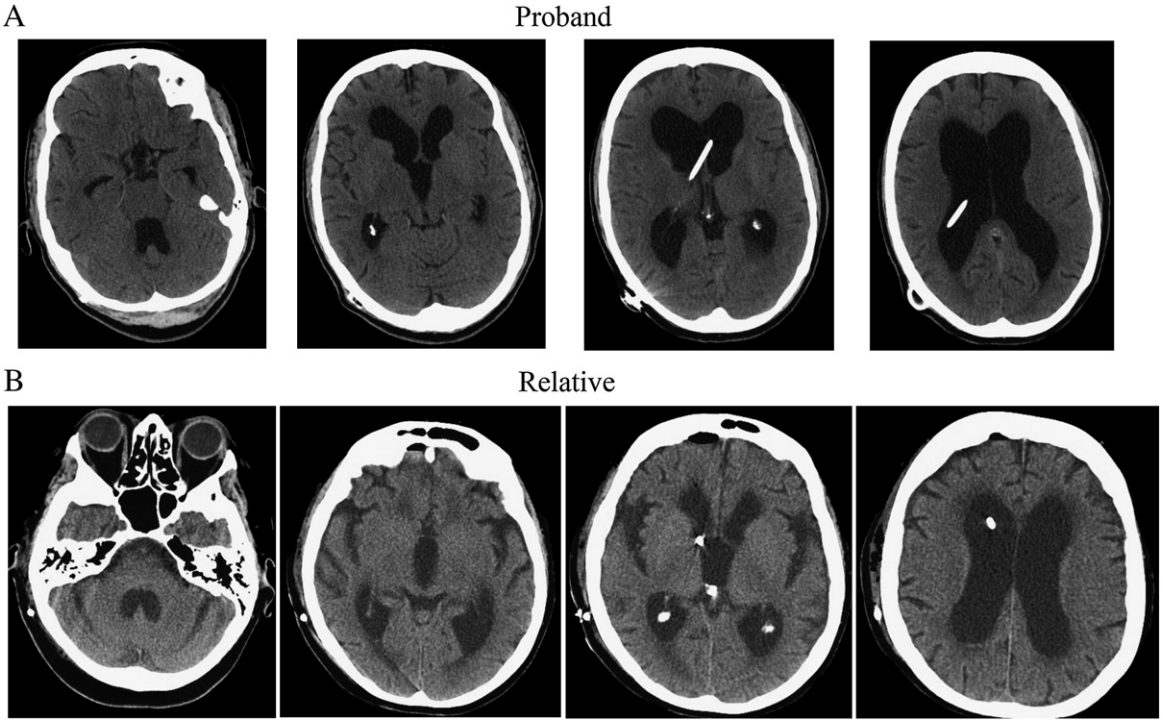

Fig. 4. Case report post-operative imaging. A) Proband post-operative CT imaging 36 months post- CSF diversion surgery demonstrating stable ventriculomegaly. B) Relative post-operative CT imaging one week post-surgery demonstrating stable ventriculomegaly and the interval placement of the shunt.

8. Familial aggregation of iNPH

In this manuscript, we present data using two methodologies suggesting that the iNPH syndrome aggregates within families.

Using a family study design among 20 iNPH probands and 21 control probands, an increased prevalence of the iNPH symptom triad was noted among the first degree relatives of iNPH probands compared to control relatives. Ten percent of iNPH pedigrees in this sample had multiple first degree relatives who exhibited ≥2 iNPH symptoms. Thus, an increased *risk* of iNPH diagnosis was identified among 7.1% of iNPH first degree relatives compared to 0.7% among control relatives. Moreover, earlier ages of onset for gait and memory impairment suggest a phenomenologically distinct presentation of iNPH symptoms among iNPH relatives.

Further, we present a novel case report of related individuals who were independently referred to our institution for evaluation and treatment of iNPH. These relatives were extensively investigated, well characterized, and demonstrated significant and sustained improvement after CSF diversion. This is the second instance [2] of related individuals who were independently referred for diagnosis and management of iNPH, which, if the rate of 1.5% observed in the Japanese population can be generalized [11], reflects a higher incidence than would be expected in the absence of familial aggregation.

It is clear that the clinical triad of gait disturbance, urinary incontinence and memory impairment are not pathognomotic of iNPH. The causes for these presenting symptoms are most often multifactorial, and often represent co-occurring disease processes. As such, the diagnosis of NPH requires careful diagnostic investigation. Increased familial loading of symptoms suggestive of NPH does not confirm the heritability of NPH, but rather, as a validated risk marker for iNPH [8], provides an impetus for a systematic detailed characterization of symptomatic and asymptomatic relatives.

There are several molecular studies assessing putative risk factors for iNPH, including allelic variation of the ApoE gene [2,14] and copy number loss of SFMBT1 [15,16]. Moreover, linkage analysis within a well characterized pedigree has implicated 19q12-13.31 and thus identified several potential candidate genes. Candidate gene approaches may provide additional evidence regarding the heritability of NPH.

Unfortunately, though we find support for familial aggregation of iNPH, our design does not allow decortication of genetic and shared environmental contributions to the putative heritability of iNPH. Further genetic epidemiology and exploration of the molecular basis for familial aggregation may lead to clearer understanding of their relative contributions to the development of iNPH. Similarly, further elucidation may provide novel treatment strategies.

9. Strengths and limitations

A strength of the family history study is the cross-generational design. Moreover, we performed additional proxy validation of iNPH proband information and demonstrated moderate to excellent validity.

The response rate for this study was 56%, which is acceptable, although the possibility of concomitant factors influencing participation and familial characteristics cannot be excluded. The sample size is limited, and requires replication with larger samples. Yet, despite the small sample, our family study provides a significant advance over previous reports of single pedigrees.

A major limitation is the use of retrospective information to assess the possibility of familial iNPH loading in the absence of additional studies to support the diagnosis of iNPH. Moreover, it is possible that iNPH probands and informants are primed to recall symptomatology consistent with iNPH. Consistent with this limitation, while heritable conditions with related symptomatology (Alzheimer's and Parkinson's disease) were assessed by the semi-structured interviews, a surprisingly low prevalence was reported.

While a definitive diagnosis of iNPH cannot be achieved retrospectively, retrospective symptom assessment has, nevertheless, been utilized and validated as an indicator of *risk* for iNPH [8]. We believe that despite its limitations, retrospective data suggesting the possibility of familial aggregateion of iNPH provides a scientific basis for further, more extensive investigations. Future studies should include direct

and blind assessment of relatives in addition to neuroimaging to further characterize the heritability of iNPH.

10. Conclusion

iNPH demonstrates familial aggregation. Approximately 7% of first degree relatives exhibit several symptoms of the iNPH triad, with multiple affected relatives in 10% of iNPH pedigrees. Symptoms presented in a phenomenologically distinct manner. A full and blind characterization of symptomatic and asymptomatic relatives should be performed to confirm heritability. High-risk studies among the relatives of iNPH probands may provide significant insight into the natural history and aetiology of iNPH, thereby providing improved detection and novel treatment strategies.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jns.2012.07.062.

Contributions

AM&MDC performed the literature review. AM collected the data. AM performed statistical analyses. AM drafted the manuscript. MDC edited and approved the final manuscript. AM had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflicts of interest

AM&MDC declare that they have no conflicts of interest related to the present study.

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