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Familial idiopathic normal pressure hydrocephalus

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ABSTRACT

Idiopathic normal pressure hydrocephalus (iNPH) is a late-onset surgically alleviated, progressive disease. We characterize a potential familial subgroup of iNPH in a nation-wide Finnish cohort of 375 shunt-operated iNPH-patients. The patients were questionnaired and phone-interviewed, whether they have relatives with either diagnosed iNPH or disease-related symptomatology. Then pedigrees of all families with more than one iNPH-case were drawn. Eighteen patients (4.8%) from 12 separate pedigrees had at least one shunt-operated relative whereas 42 patients (11%) had relatives with two or more triad symptoms. According to multivariate logistic regression analysis, familial iNPH-patients had up to 3-fold risk of clinical dementia compared to sporadic iNPH patients. This risk was independent from diagnosed Alzheimer's disease and *APOE ε4* genotype.
This study describes a familial entity of iNPH offering a novel approach to discover the potential genetic characteristics of iNPH. Discovered pedigrees offer an intriguing opportunity to conduct longitudinal studies targeting potential preclinical signs of iNPH.

1. Introduction

Idiopathic normal pressure hydrocephalus (iNPH) is a late-onset progressive brain disease with disturbance in cerebrospinal fluid (CSF) dynamics. Clinical characteristics include a triad of deteriorated gait, urinary incontinence and cognitive impairment, together with enlarged brain ventricles [1–3]. Symptoms can be alleviated with a CSF shunt, but the long term impact seems modest only [3–6].

The reported annual incidence of iNPH varies from 0.5/100,000 to 5.5/100,000. The estimated prevalence is 22/100,000 increasing with age and in the elderly populations it varies from 0.5% up to 5.9% [7–10].

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The pathophysiological basis of iNPH remains elusive [1,11]. Alzheimer's disease (AD)-related neuropathological findings and vascular lesions are common, and concomitant AD may hamper the initial benefit from a shunt [4,5,12]. Shunting and iNPH itself may influence the CSF dynamics of amyloid-β (Aβ) clearance [13–15].

Portenoy et al. in 1984 were the first to present iNPH as a potentially inherited disease.

[16]. A total of 8 iNPH-families, reported previously suggest a familial subgroup of iNPH with potential autosomal dominant inheritance (Table 1[16–22]) including a family with essential tremor and concomitant iNPH (ETINPH) with linkage to 19q12–13.31 [15,16]. Still, little is known about the familial characteristics of iNPH.

We first analyzed the overall incidence of shunt-operated iNPH in the Finnish population, and then identified potential iNPH families by disease history in the pedigrees.

2. Methods

2.1. Data collection and selection of patients

In Finland, all surgical procedures on CSF disorders are carried out in six neurosurgical units, with a defined catchment population (Supplementary Table 1). The patient registries of the six units were retrospectively screened to identify all patients shunted due to NPH. Potential patients were searched based on both operative procedure codes and diagnostic code (ICD 10; G91.2). Patient records were reviewed by a neurosurgeon to exclude any potential secondary etiology including obstructive hydrocephalus. Overall 1095 patients with possible or probable iNPH [3] were included in the study (Supplementary Fig. 1). The patients were shunted between 1993 and 2014 the timeframe varying between neurosurgical units (Supplementary Table 1, Supplementary Fig. 1).

Patients were sent an informed consent with 6-page questionnaire containing patient information form (including smoking, use of alcohol, physical performance, chronic and previous diseases, current medication, surgeries performed) and iNPH-item (shunt and shunt response, other diagnosed neurodegenerative diseases, medication for memory disease, iNPH-symptoms and family anamnesis with contact information of relatives willing to participate in the study). Altogether 616 questionnaires (56%) fulfilled by the patient or next of kin were returned.

All questionnaire data from patients with informed consent and adequately filled form (n = 469; 42.9%) was screened by a neurosurgeon to further confirm the exclusion of any potential secondary etiology of NPH not noted in primary selection. Criteria resulting in exclusion were subarachnoid hemorrhage (SAH), intracerebral hemorrhage, meningitis or craniotomy prior to shunt surgery as well as aqueduct stenosis or another obstruction potentially affecting CSF-dynamics. Unwillingness to participate in genealogy or offer family data was an additional exclusion criterion. Based on this, 94 patients were excluded from further analysis limiting the final number of patients to 375 (34% of the original sample of 1095) with probable iNPH [3].

Patients with reported familial iNPH-symptomatology (n = 60) were approached in terms of phone interviews. The aims of each interview were to exclude other disorders causing the triad symptoms and confirm the information reported on the questionnaire. Furthermore, all available healthy relatives and relatives with triad symptoms (Table S1) were first contacted by the proband. After that, the relatives were sent an informed consent and identical questionnaire (150 out 204 returned, 74% response rate) in order to validate the information, to define their interest in participating in the study and give a blood sample for genetic study. The relatives reporting possible iNPH related symptoms were also phone interviewed.

Relying on the data gathered from the questionnaire and phone interviews, a pedigree of each iNPH-family was drawn (Fig. 2). The level of information indicating familial iNPH was divided into two categories: 1) probable familial iNPH (at least one relative with shunt due to iNPH), and 2) possible familial iNPH (at least one relative with ≥2 self-reported triad symptoms) [3,23]. Patients fulfilling neither of the two categories were grouped as sporadic iNPH.

2.2. Geographical analysis

For geographical evaluation, iNPH patients shunted from 2010 until 2012 (comparable data available from all participating units, n = 144 out of 375) were categorized by home county. For yearly incidence, a mean number of shunt-operated iNPH patients collected during three consecutive years was divided by a mean number of population aged higher than 60 years during the corresponding time frame with regional presentation (Fig. 1A). Additionally, the birth municipalities of familial (n = 54, Fig. 1B) and sporadic (n = 268, Fig. 1C) patients were graphically examined.

2.3. APOE-genotyping

Genomic DNA was extracted from venous blood samples using QIAamp DNA blood mini extraction kit (QIAGEN). *APOE* genotyping

Table 1
Previous studies and case reports found in systematical search of the literature.[a]

Study	Number of affected pedigrees discovered	Number of familial iNPH-cases (shunt/possible)	Additional information
Portenoy et al. (1984) [16]	1	2 (2/0)	67-year-old man and his 74-year old sister both with shunt-responsive iNPH
Zhang et al. (2008 and 2010) [17,18]	1	3 (2/1)	Two family members with confirmed diagnosis and one with characteristic symptoms based on family interviews. Moreover, symptomatic essential tremor affected all of these patients and 11 other relatives.
Takahashi et al. (2011) [21]	1	8 (4/4)	Four patients had clinically documented features with ventriculomegaly. In addition four other family members with interview-based symptomatology were discovered.
Cusimano et al. (2011) [19]	1	2 (2/0)	Sisters who lived together their entire lives being exposed to similar environmental factors. They both developed clinical iNPH with a favorable post-shunt outcome.
McGirr and Cusimano (2013) [20]	3	8 (2/6) 4 (3/1)	Family history of 20 shunted patients and 21 controls was mapped. Questionnaire data of 291 first-degree relatives from 41 families was collected and compared in a case-control setting. 7% of patients had at least one relative with probable iNPH. Also additional family with 4 diagnosed (3 shunted) iNPH patients was reported.
Liouta et al. (2014) [22]	1	4 (2/2)	71 and 73-year-old sisters both with early-onset symptomatology and beneficial response to shunt. Their 45 and 48-year-old daughters are both suffering from urinary incontinence of unknown etiology with empty sella and enlarged subarachnoid spaces in MRI.
Total	8	31	

[a] Literature research was conducted on Medline and Scopus with key words "normal pressure hydrocephalus" AND ("family" OR "familiality" OR "familial aggregation" OR "genealogy" OR "sibling" OR "pedigree" OR "inheritance" OR "genetics") published until 1-MAR-2015.

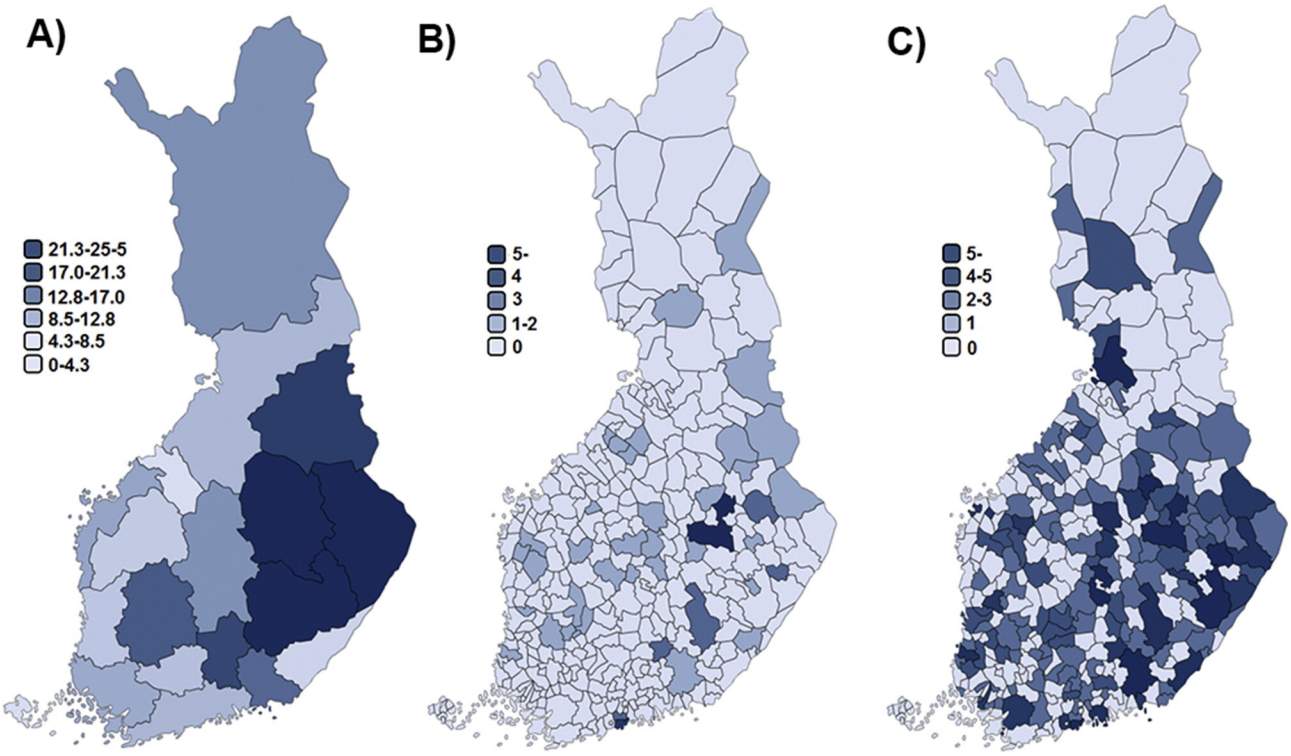

Fig. 1. A) Regional distribution of 144 iNPH patients shunted between 2010 and 2012. The three years mean number of shunted patients was divided by the mean of local population aged over 60 during the corresponding years. Presented as mean incidence per 100,000 inhabitants. B) Birth municipalities of 54 familial iNPH-patients. C) Birth municipalities of 268 sporadic iNPH-patients.

was determined by polymerase chain reaction using TaqMan genotyping assays (Applied Biosystems (ABI), Foster City, CA, USA) for two single-nucleotide polymorphisms (rs429358 and rs7412) and an allelic discrimination method on the ABI 7000 platform [24]. All the relatives participating in the study were sent blood vials and information letter via mail. Blood samples were collected at local health centers. Overall *APOE* was genotyped from 357 shunted patients (95%) and 150 relatives.

2.4. Statistical analyses

Only shunt operated iNPH patients (n = 375) were included into the statistical analyses. The variables were compared between familial and sporadic groups by performing Chi-square test for categorical variables and Student's *t*-test (normally distributed) or non-parametric Mann-Whitney *U* test (non-normally distributed) for continuous variables. Multivariate logistic regression analysis was performed to account for confounding by other clinical variables in the analysis of differences between familial and sporadic iNPH-patients. All the variables analyzed were based on the questionnaire data except the APOE-analyses and in-depth characterization in Table 3. To avoid bias, symptomatic relatives were excluded from the analyses and family anamnesis was only used for grouping shunt-operated iNPH-patients. Variables were analyzed between three groups: 1) "Sporadic iNPH" (n = 315, shunt-operated iNPH-patients with no self-reported familial symptomatology), 2) "Possible familial iNPH" (n = 60, shunt-operated iNPH-patients with at least one relative with ≥2 self-reported triad symptoms) and 3) "Probable familial iNPH" (n = 18 out of 60 possible familial iNPH patients, shunt operated iNPH-patients with at least one diagnosed iNPH-relative). The standard $p = 0.05$ was considered to be the threshold value of statistical significance. SPSS statistical software (version 22.0, SPSS Inc., Chicago, Illinois) was used in the analyses.

2.5. Ethical issues

The study was approved by the Kuopio University Hospital (KUH) Research Ethics Committee. All patients and their relatives included in the study gave an informed consent.

3. Results

The age-adjusted yearly incidence of shunt-operated iNPH varied from 0 to 26 cases per 100,000 inhabitants aged over 60 and was highest in Eastern Finland (Fig. 1A).

Altogether 60 patients (16% out of 375) had a possible or probable familial iNPH; 18 (4.8%) had probable (shunted) iNPH relative and 42 possible iNPH-relative (Table 2). Gender distribution was equal in familial and sporadic groups. The familial group was three years older at shunting ($p = 0.008$). No statistical difference was found in alcohol usage or smoking between the groups. No significant difference was discovered in the frequency of *APOE* ε4 allele between familial and sporadic iNPH and controls. The self-reported benefit (for any of the iNPH-related symptoms) for shunt-surgery was reported 100% among patients with probable familial iNPH, 90.9% among patients with possible familial iNPH and 92.1% in sporadic group ($p = 0.788$, Table 2).

Overall 12 shunted and 42 possible iNPH pedigrees were discovered (Tables 2 & 3). Shunted relatives were mainly first-degree [15/19 siblings (9 sisters, 6 brothers; one patient had two shunted siblings), a father, a son and an uncle] as well as other symptomatic relatives [30/59 (51%) siblings (16 sisters, 14 brothers) 24/59 (41%) parents (17 mothers, 7 fathers), a daughter, a cousin, two aunts and an uncle]. Twelve shunted relatives were also index patients.

Clinical characteristics of 12 pedigrees with at least two shunted patients were further examined by utilizing available registries (Table 3). Six out of 19 relatives had *APOE* ε4 allele. All familial iNPH patients with available questionnaire or registry data were shunt responsive.

Table 2
Comparison of questionnaire data by familial symptomatology in patients with diagnosed iNPH (n = 375).

	A) Sporadic iNPH (n = 315)	B) Possible familial iNPH (n = 60)	C) Probable familial iNPH (n = 18/60)	*p* (*A* vs *B*)	*p* (*A* vs *C*)
Age at shunt (mean and SD)	70.3 (±7.7)	73.2 (±6.6)	74.06 (±6.68)	**0.008**[a]	**0.046**[a]
Shunt response (self reported)	267/290 (92.1%)	50/55 (90.9%)	17/17 (100%)	0.788	0.381
Follow-up time (from shunt until the questionnaire)	4.2 (±3.9)	3.4 (±2.6)	3.6 (±2.3)	0.243[b]	0.921[b]
Sex (F/M)	170/145	32/28	7/11	1.000[c]	0.233
BMI (mean and SD)	28.6 (±4.8)	28.2(±5.3)	27.7 (±5.7)	0.518[a]	0.502[a]
Smoking					
-Smoker	15/312 (4.8%)	2 (3.3%)	0	0.431[c]	0.626
-Ex-smoker	79/312 (25.3%)	11 (18.3%)	4/18 (22.2%)		
Consumes alcohol	109/313 (34.8%)	17 (28.3%)	7/18 (38.9%)	0.373[c]	0.801
Complete triad	118 (37.5%)	32 (53.3%)	7/18 (38.9%)	**0.030**[c]	1.000
Prevalence of *APOE* ε4	87/298 (29.2%)	15/59 (25.4%)	6/17 (35.3%)	0.637[c]	0.786
Memory and neurological comorbidities					
-Diagnosed AD	43/295 (14.6%, 51.2% *APOE* ε4)	13/60 (21.7%, 33.3% *APOE* ε4)	3/18 (16.7%)	0.176[c]	1.000[c]
-Other diagnosed neurodegenerative disorder	23/281 (8.2%)	6/59 (10.2%)	4/18 (22.2%)	799[c]	0.067[c]
-Clinical dementia	56 (17.8%)	22 (36.7%)	7/48 (38.9%)	**0.001**[c]	**0.035**[c]
-"I am having problems with memory"	186/289 (64.4%)	48/59 (81.4%)	13/18 (72.2%)	**0.014**[c]	0.615[c]
-Memory drug	44/307 (14.3% %)	13/58 (22.4%)	3/18 (16.7%)	0.173[c]	1.000[c]
-Epilepsy	18 (5.7%)	4 (6.7%)	2/18 (11.1%)	1.000	0.613[c]
-Parkinsonism	13 (4.1%)	1 (1.7%)	1/18 (5.6%)	0.485[c]	1.000[c]
Cardiovascular comorbidities					
-Hypertension	175 (55.6%)	41 (68.3%)	15/18 (83.3%)	0.087[c]	**0.026**[c]
-Coronary disease	62 (19.7%)	9 (15.0%)	2/18 (11.1%)	0.474[c]	0.542[c]
-Stroke/TIA	45 (14.3%)	7 (11.7%)	0/18	0.687[c]	0.147[c]
-Venous thrombosis	18 (5.7%)	8 (13.3%)	2/18 (11.1%)	**0.048**[c]	0.613[c]
-Diabetes	111 (35.2%)	18 (30.0%)	4/18 (22.2%)	0.463[c]	0.316[c]
Other comorbidities					
-Rheumatoid arthritis	17 (5.4%)	4 (6.7%)	1/18 (5.6%)	0.758[c]	1.000[c]
-Other rheumatoid disease[d]	13 (4.1%)	8 (13.3%)	1/18 (5.6%)	**0.010**[c]	1.000[c]
-Spinal stenosis	32 (10.2%)	12 (20.0%)	6/18 (31.3%)	**0.046**[c]	**0.010**[c]
Performance					
-Is able to fill the questionnaire independently	156/311 (50.2%)	21/60 (35.0%)	8/18 (44.4%)	**0.035**[c]	0.809[c]

[a] *t*-Test.
[b] Mann-Whitney *U* test.
[c] χ^2-test.
[d] These include fibromyalgia (n = 6), polymyalgia rheumatica (n = 4), psoriasis (n = 2) and 9 non-specific cases.

Table 3
Characteristics of 12 iNPH-pedigrees with multiple shunted family members.

	Age at shunt	Sex (M/F)	Full triad	Clinical dementia	Shunt responsiveness	*APOE*	Brain biopsy Aβ	Brain biopsy *Tau (AT8)	Brain biopsy p62	Co-morbidities	MMSE (preop)	Shunted relatives	Propable iNPH-relatives in family (≥2 symptoms)
I	80	M	1	1	1	33	N/A	N/A	N/A		N/A	Son	
II	80	M	1	0	1	34	1	0	1	PD as follow-up diagnosis	24	Siblings	Mother
	75	F	0	0	1	33	0	0	1		25		
III	79	M	1	1	1	33	0	0	0	Symptomatic epilepsy	12	Brother	
IV	73	F	1	0	1	34	1	0	0		28	Siblings	Sister
	69	F	0	0	1	34	N/A	N/A	N/A		N/A		
V	84	M	1	1	1	33	1	1	(+)		18	Siblings	
	76	F	1	1	1	33	N/A	N/A	N/A		N/A		
VI	70	F	0	0	1	33	0	1	1	AT8- positive in frontal cortical biopsy, migraine	27	Identical twins	
	71	F	0	0	1	33	0	0	1		28		
VII	66	F	1	0	1	33	N/A	N/A	N/A		24	Sister (deceased)	
VIII	87	M	1	1	1	33	N/A	N/A	N/A		N/A	320 is nephew of 220	
	67	M	1	1	1	33	N/A	N/A	N/A	Suspected vascular dementia	N/A		
IX	67	M	0	0	1	23	0	0	1		22	Father (deceased)	
X	73	M	0	1	1	34	N/A	N/A	N/A	AD		Brother and sister (deceased)	
XI	64	M	1	1	1	34	1	0	1	FTD	22	Siblings	
	68	M	1	0	1	33	N/A	N/A	N/A		25		
XII	74	M	0	0	1	34	1	0	0		28	Siblings	
	74	F	1	0	1	33	1	0	1		21		

Cortical brain biopsies and validated clinical and follow-up data are available from KUH patients. *Tau indicates hyperphosphorylated tau detected by AT8 antibody. Symptomatic and cognitive status of other patients relies on questionnaire- and interview-based data. All subjects with any clinical data are clinically confirmed iNPH-patients. With respect to pedigrees I, III, VII & X the shunt status of relatives has been confirmed by medical interviews and available patient registry data. *Patient XII-B is included in Kuopio NPH-registry but did not respond to the questionnaire and was not treated as an index patient.

With respect to symptomatology and cognitive status, the prevalence of a complete triad of NPH-related symptoms was more frequent in familial group (53.3% vs. 37.5%; $p = 0.03$) as well as subjective memory problems ($p = 0.014$) compared to sporadic iNPH. Clinical dementia was more common in familial (36.7%) than sporadic patients (17.8%; $p = 0.001$). AD was the most frequent specific clinical diagnosis of dementia. Furthermore, spinal stenosis, venous thrombosis and rheumatoid diseases were more common in familial group (Table 2). According to multivariate analysis, only clinical dementia and rheumatoid manifestations remained significantly more frequent in the familial than sporadic iNPH (Table 3).

In a subgroup analysis of patients with shunt-operated iNPH-relative, risk of clinical dementia remained significant even when adjusted to age, sex *APOE* ε4 and concomitant AD ([OR] 4.3; 95% CI 1.1–19.2). Interestingly, according to multivariate analysis hypertension and spinal stenosis were the most common in this group (Tables 2 & 4). Rheumatoid diseases, venous thrombosis, and prevalence of complete triad did not reach statistical significance.

The genograms of iNPH-families were sketched from each familial patient, the most interesting of them displayed in Fig. 2. A number of shunted iNPH-siblings and even identical twins both with shunt-responsive iNPH in a year interval were discovered.

In the Kuopio University Hospital (KUH) area, 160 iNPH-patients were included in our cohort, those of whom twelve (7.5%) had at least one shunted relative and fourteen (8.8%) at least one possible iNPH-relative. The mean age was 76.6 years and only six patients were under 65. Since λ_R is the risk of disease in the relative of index patient, divided by general prevalence that is:

$$\lambda = \frac{\Pr(D|\mathrm{AR})}{\Pr(D)}$$

A rough estimate of λ_R in KUH-area would be ~200 on all familial subjects when using the local prevalence of 65 + population. However, based on the KUH NPH-registry, the overall prevalence is much higher (data not shown). Still, extrapolation would diminish the portion of familial iNPH-patients and thus absolute percentage is the most unbiased estimate. To get an accurate λ_R, more complete pedigree data and epidemiological numbers are required.

4. Discussion

This study is the first to evaluate familial occurrence of iNPH in a nation-wide cohort of shunt-operated iNPH patients. Apart from individual case reports, only McGirr and Cusimano have used a systematic approach yet comparing the occurrence of iNPH related symptoms in relatives of iNPH-patients to relatives of non-INPH controls [20]. Furthermore, the current study with a notable number of patients more likely detects the potential specific characteristics of the familial iNPH.

Our results confirm a familial entity of iNPH with a notable prevalence. Since clinical dementia seems to be more frequent in the familial group, the proposed familial iNPH may be clinically more aggressive than the sporadic iNPH. This increased risk of dementia seems to be independent from clinically diagnosed AD and *APOE* ε4 genotype raising further suspicion of iNPH as an independent entity to potentially cause dementia even when treated with current standards [4].

4.1. Characteristics of familial subgroup

The most significant finding was the extent to which possible familial iNPH occurs. Every sixth (16%) of the study patients had at least one relative with shunt-operated or possible iNPH. The number of patients with possible iNPH relative (16%) was close to that previously reported by McGirr and Cusimano (2/20; 10%) [20]. Nearly all shunted and symptomatic relatives were first-degree. However, the questionnaire and interview-based approach is suboptimal to reach more distant relatives and thus a major potential source of error. The number of potential iNPH-pedigrees discovered was surprisingly high (12 shunt-operated, 42 possible) since only 8 separate pedigrees have been described previously (Table 1).

Comparing the familial group to sporadic, we discovered significant differences concerning the prevalence of complete triad, memory problems and clinical dementia referring to potentially more severe symptomatology among familial patients. Clinical dementia was even highlighted in the subgroup analysis with multiple adjustments regardless of modest sample size. Unexpectedly the mean age at shunting in the familial patients tended to be higher opposing most of the other hereditary forms of neurodegenerative diseases manifesting usually earlier than sporadic forms. Unfortunately, we were not able to define the exact onset-age when the first clinical symptoms appeared. Furthermore, patients with positive family history might have been more likely interested in participating in the study. Despite more frequently reported clinically diagnosed dementia in the familial group, differences in functional capacity and residency were relatively minor.

4.2. Potential sources of error

The main sources of potential error were mainly questionnaire-based data and the decreased cognitive performance in a large number of patients. Only 47% of the patients could fill the entire form independently thus in half of the patients the information was given by next of kin. Furthermore, we believe that the patients with the lowest capacity were more often unable to return the questionnaire and the patients with iNPH or iNPH related symptoms in the family may have been more

Table 4
Logistic regression analysis comparing possible familial iNPH (n = 60), and probable familial iNPH (n = 18 out of 60) with sporadic iNPH (n = 315) as a reference.

		Possible familial iNPH (n = 60)			Probable familial iNPH (n = 18 out of 60)		
Comorbidity	Model	OR	95% CI	*p*	OR	95% CI	*p*
Dementia	Univariate	2.678	1.471–4.875	0.001	2.943	1.093–7.926	0.033
	Multivariate*	2.693	1.188–6.107	0.018	4.311	1.103–19.224	0.047
Hypertension	Univariate	1.726	0.959–3.107	0.069	4.000	1.135–14.093	0.031
	Multivariate**	1.690	0.914–3.127	0.095	4.116	1.125–15.053	0.032
Venous thrombosis	Univariate	2.483	0.976–6.316	0.056	2.062	0.440–9.669	0.358
	Multivariate**	2.311	0.900–5.937	0.082	2.230	0.390–12.751	0.367
Rheumatoid manifestation	Univariate	3.833	1.448–10.146	0.007	1.367	0.169–11.068	0.770
	Multivariate**	3.599	1.399–9.676	0.011	1.494	0.140–15.903	0.739
Spinal stenosis	Univariate	2.052	0.956–4.404	0.065	4.422	1.554–12.585	0.005
	Multivariate**	1.975	0.914–4.265	0.083	3.416	1.073–10-874	0.038
Complete triad	Univariate	1.908	1.094–3.327	0.023	1.062	0.401–2.816	0.903
	Multivariate**	1.346	0.704–2.573	0.369	0.516	0.145–1.835	0.306

* Multivariate analysis included adjustment to sex, age, other comorbidities, APOE ε4 and diagnosed AD.
** With respect to other comorbidities, *APOE* ε4 and diagnosed AD were excluded from multivariate model due to limited sample size and irrelevant statistical effect (data not shown).

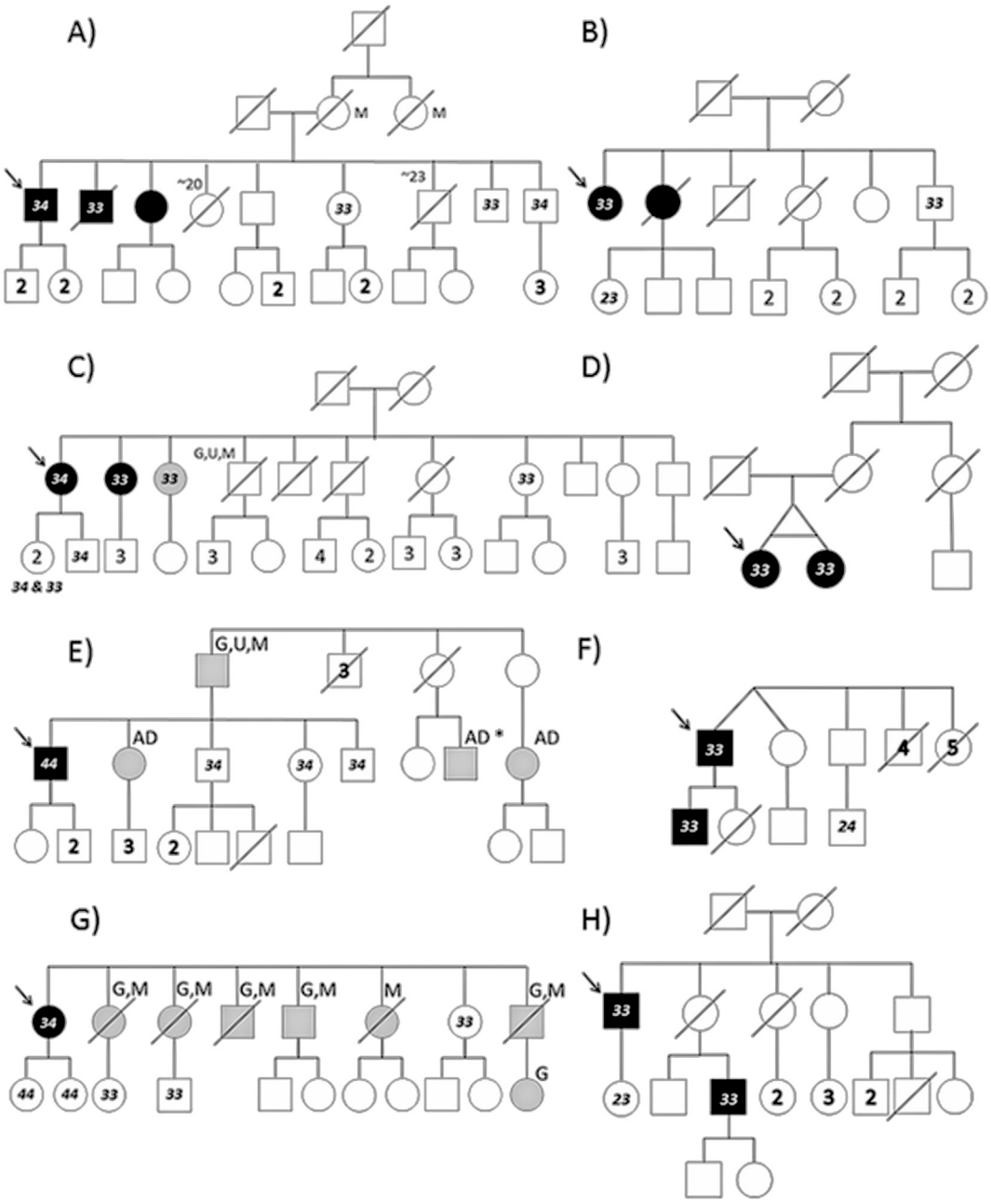

Fig. 2. Eight multiplex iNPH-pedigrees. Black symbols indicate patients with shunt/diagnosed iNPH. Potential iNPH/AD-patients are colored gray. Symptoms of the Hakim triad are marked with G (gait problems), U (urinary incontinence) and M (memory deficit). *APOE* alleles are included in binumeric form when available. Pedigrees A–C present multiple siblings affected. Additionally, history of impaired memory on mother's side was reported with respect to pedigree A. Pedigree D: identical twins both with diagnosed, shunt-responsive iNPH. The twins had lived together with similar environmental exposure. E & G: two pedigrees with multiple affected first-degree relatives and three siblings with probable AD. This finding suggests that there may be common inherited elements manifesting as various, parallel clinical types of neurodegeneration. *APOE* ε4 was detected in both of these families. Pedigrees F & H indicate longitudinal expression of familial iNPH, referring to autosomal (dominant) inheritance.

inclined to respond. This is also suspected by the very high reported response rate (92%) for the shunt, especially in those with more than one shunted patients in the family. Also, we were not able to confirm iNPH radiologically in the relatives with possible iNPH. Also, low response rate and strict etiological exclusion criteria presumably leave a number of potential pedigrees yet to be discovered. In addition, we were not able to screen the families of the deceased iNPH patients limiting generalizability of our results and warranting further prospective study.

4.3. Comorbidities

The familial iNPH cases were expected to have less co-morbidities. Venous thrombosis was more common in the familial group yet not in confirmed pedigrees. Interestingly, hypertension – a common comorbidity in patients with iNPH [25] – was even more frequent in familial cases even after multiple adjustments. Overall, the role of vascular factors affecting iNPH etiology in general remains unknown. Bateman & Siddique discovered recently that patients with chronic hydrocephalus had narrower sinuses with increased venous pressure and weakened blood flow [26]. On the other hand, perivascular pathways and e.g. cribriform lamina have shown to play a role as a potential compensatory or even primary route for CNS fluid absorption [27].

Regardless of the increased number of reported clinical dementia in familial iNPH patients, no significant difference was discovered in the prevalence of clinical AD. This is supported by the multivariate analyses indicating that the risk of dementia seems to be independent from AD,

APOE ε4, age and sex. However, higher susceptibility to amyloid deposition in all patients with iNPH is well documented corresponding to our findings as well. Overall, the prevalence of clinically diagnosed AD in both the familial and the sporadic group (22% vs. 15%) was relatively high comparing with the previous epidemiological studies on AD and considering the mean age of our study population. Evans et al. found the prevalence of probable AD in age categories of 64–75 years, 75–84 years and 85 + years to be 3.0%, 18.4% and 47.8%, respectively [28]. The prevalence of AD-related neuropathological findings among iNPH-patients varies from 20% to 70% depending on the detection method and cohort [9].

4.4. Perspectives into epidemiology

Notable geographical variation in the incidence of shunt-operated iNPH patients was discovered, concentrating in Eastern Finland (Fig. 1). To exclude the effect of regional variation in the timeframe of recruitment, only patients from the years with comparable data were used in this analysis. The lower response rates in the Southern and Northern Finland may have some confounding effect. Furthermore, regional differences in the primary diagnostics and variable diagnostic criteria for the surgery with the insidious nature of iNPH are potential sources of error, yet hardly the sole cause of the detected variation. Heterogeneous epidemiological numbers reported on cohorts with different population samples also support the hypothesis of potential genetic variation despite considerable methodological differences [7–10].

There is only a slight risk developing iNPH before senescence. Due to limited attendance and potential diagnostic heterogeneity, the overall epidemiological rates are surely underestimated. This is supported by Jaraj et al. emphasizing that the prevalence of iNPH rapidly emerges with age being up to 6% in population aged over 80 [9]. Thus, more tailored epidemiological approaches with uniform inclusion criteria and age-adjustment are required. For example, when evaluating siblings and relative recurrence risk ratios, overall prevalence of iNPH gives extremely high values due to age distortion.

In addition, birth municipalities of familial and sporadic iNPH-patients were graphically illustrated. Similar east-bound trend remained in birthplaces of both groups. However, no timeframe correction was used which may skew the geographical incidence of iNPH families. This requires further study, since biased timeframe, and regional variation in the diagnostics and response rates are potential cofounders.

Pastinen and colleagues investigated Finnish disease heritage mutations resulting in regional clustering in both more common and rare mutations [29]. Assumedly, this variation is due to sub-isolates and multiple bottlenecks formed, enriching such alleles regionally. The regional accumulation discovered by us, supports the hypothesis of potential genetic factors related with iNPH. The cases were examined in relation to regional population aged over 60 years since symptomatic iNPH rarely manifests at earlier age. This also reduces the bias caused by regional differences in age composition yet the same trend persisted in analyses based on total population values. Weighted age-adjusted regional analysis was unfortunately impossible due to the limited number of patients.

4.5. APOE and other genetic aspects

In line with Pyykkö et al., no significant difference was discovered in the prevalence of *APOE* ε4 in iNPH patients compared with control population [30]. Based on our current findings, previous study and modest regional variation found in *APOE* polymorphisms, it seems that ε4 allele may be overexpressed in iNPH with concomitant AD but does not have a key role in the pathomechanism of solitary iNPH [30,31]. As only few studies have yet investigated iNPH with genomic approach [17,18,32] and frequent comorbid AD is well-documented [6,11], further studies targeting the genes of amyloid cascade [33–35] and genome-wide approaches are required. Shunted siblings are most likely to carry potential mutations playing the key role in iNPH and thus require more accurate methodologies focusing on sequencing and functional genomics. Recognizing more potential iNPH-pedigrees as well as more in-depth genealogy searching for potential common bloodlines are also taken into consideration.

4.6. Scientific significance and future perspectives

To conclude, the multiple iNPH-families discovered, offer a benchmark from which genetic studies can be considered. Analogically, our approach with detected geographical variability and multiple pedigrees discovered has some similar characteristics compared to early studies of Finnish familial intracranial aneurysms [36]. With respect to our pedigrees; both Mendelian and multifactorial inheritance ought to be considered. Rather late onset age of iNPH and incomplete penetrance of potential alleles are also aspects taken into consideration. The first-degree relatives offer an intriguing approach concerning both genomic and preclinical longitudinal studies. Iseki et al. [8] performed a large-scale neuroradiological study examining possible preclinical findings of iNPH [8]. Authors suggested asymptomatic ventriculomegaly being a potential preclinical sign of iNPH. Additionally, Liouta et al. introduced daughters of two iNPH-sisters both, already in their forties, presented with long-lasting urinary incontinence and ventricular enlargement with empty sella [22]. Since pathophysiological knowledge of iNPH has remained elusive during the past five decades, novel, unprejudiced approaches are required both in the field of iNPH and neurodegeneration.

5. Conclusions

1. There seems to be a familial subgroup of iNPH. Family history is worth screening both in research and in clinical setting. The knowledge of existing familial risk might hasten the otherwise late diagnosis on iNPH patients thus accelerating access to treatment.
2. More prevalent risk of dementia in familial group seems to be independent from AD and *APOE* ε4 supporting iNPH to have potential specific genetic pathways.
3. Our cohort and findings offer a novel opportunity to conduct genetic studies and identify potential preclinical diagnostic and prognostic factors for iNPH.

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Conflicts of interest disclosure

The authors have nothing to report. All the authors have fulfilled appropriate disclosure forms as requested.

Author contributions

Conception and design of the study: A.M.R., H.S., M.H., M.K., J.E.J. and V.L.

Data collection: J.H., S·Ka., S·Ko., M.O., C.A., J.F., J.R., A.R., M.K., K.L., O.T.P., A.M.K., and V.L.

Analysis and interpretation of the data: J.H., S·Ka., S·Ko. M.P., A.M.R., M.H., S.H., M.K., J.E.J. and V.L.

Writing of the manuscript: J.H., S·Ka., S·Ko. and V.L. All other authors offered comments and suggestions to the initial version of the manuscript and endorsed the submitted version.

All authors, upon request, had full access to all the data reported in the manuscript.

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