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Familial idiopathic normal pressure hydrocephalus

Joel Huovinen [a], Sami Kastinen [a], Simo Komulainen [a], Minna Oinas [b], Cecilia Avellan [b], Janek Frantzen [c], Jaakko Rinne [c], Antti Ronkainen [d], Mikko Kauppinen [e], Kimmo Lönnrot [f], Markus Perola [g,h], Okko T. Pyykkö [a], Anne M. Koivisto [i], Anne M. Remes [i], Hilkka Soininen [i], Mikko Hiltunen [i,j], Seppo Helisalmi [i], Mitja Kurki [a,k,l,m], Juha E. Jääskeläinen [a], Ville Leinonen [a,*]

[a] Department of Neurosurgery, Kuopio University Hospital, Institute of Clinical Medicine, University of Eastern Finland, Kuopio, Finland
[b] Department of Neurosurgery, University of Helsinki, Helsinki University Hospital, Finland
[c] Clinical Neurosciences, Department of Neurosurgery, Turku University Hospital, Turku, Finland
[d] Department of Neurosurgery, Tampere University Hospital, Tampere, Finland
[e] Department of Neurosurgery, Oulu University Hospital, Oulu, Finland
[f] South Ostrobothnia Central Hospital, Seinäjoki, Finland
[g] National Institute for Health and Welfare, Finland
[h] University of Helsinki, Helsinki, Finland
[i] Unit of Neurology, Institute of Clinical Medicine, University of Eastern Finland, Department of Neurology, Kuopio University Hospital, Kuopio, Finland
[j] Institute of Biomedicine, University of Eastern Finland, Kuopio, Finland
[k] Analytical and Translational Genetics Unit, Department of Medicine, Massachusetts General Hospital, USA
[l] Program in Medical and Population Genetics, Broad Institute of MIT and Harvard, USA
[m] Stanley Center for Psychiatric Research, Broad Institute for Harvard and MIT, USA

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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].

* Corresponding author at: Department of Neurosurgery, Kuopio University Hospital, P.O. Box 100, FIN-70029 KYS, Finland.
E-mail addresses: joel_huovinen@hotmail.com (J. Huovinen), samikas@student.uef.fi (S. Kastinen), simokom@student.uef.fi (S. Komulainen), minna.oinas@hus.fi (M. Oinas), cecilia.avellan@hus.fi (C. Avellan), janek.frantzen@tyks.fi (J. Frantzen), jaakko.rinne@tyks.fi (J. Rinne), antti.ronkainen@pshp.fi (A. Ronkainen), mikko.kauppinen@ppshp.fi (M. Kauppinen), kimmo.lonnrot@epshp.fi (K. Lönnrot), markus.perola@thl.fi (M. Perola), okko.pyykko@gmail.com (O.T. Pyykkö), anne.koivisto@kuh.fi (A.M. Koivisto), anne.remes@uef.fi (A.M. Remes), hilkka.soininen@uef.fi (H. Soininen), mikko.hiltunen@uef.fi (M. Hiltunen), seppo.helisalmi@uef.fi (S. Helisalmi), mitja.kurki@gmail.com (M. Kurki), juha.e.jaaskelainen@kuh.fi (J.E. Jääskeläinen), ville.leinonen@kuh.fi (V. Leinonen).

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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.