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Prevalence of Schizophrenia in Idiopathic Normal Pressure Hydrocephalus

BACKGROUND: Idiopathic normal pressure hydrocephalus (iNPH) is a progressive and potentially treatable neurodegenerative disease affecting elderly people, characterized by gait impairment and ventricular enlargement in brain imaging. Similar findings are seen in some patients with schizophrenia (SCZ).

OBJECTIVE: To determine the prevalence of SCZ among patients suffering from probable or possible iNPH and the specific effects of comorbid SCZ on the outcome of the cerebrospinal fluid (CSF) shunting.

METHODS: All medical records of the 521 iNPH patients in the NPH registry were retrospectively analyzed from 1991 until 2017. The prevalence of comorbidity of SCZ was determined and compared to that of general aged (≥65 yr) population in Finland.

RESULTS: We identified a total of 16 (3.1%) iNPH patients suffering from comorbid SCZ. The prevalence of SCZ among the iNPH patients was significantly higher compared to the general population (3.1% vs 0.9%, $P < .001$). All iNPH patients with comorbid SCZ were CSF shunted and 12 (75%) had a clinically verified shunt response 3 to 12 mo after the procedure. The CSF shunt response rate did not differ between patients with and without comorbid SCZ.

CONCLUSION: SCZ seems to occur 3 times more frequently among iNPH patients compared to the general aged population in Finland. The outcome of the treatment was not affected by comorbid SCZ and therefore iNPH patients suffering from comorbid SCZ should not be left untreated. These results merit validation in other populations. In addition, further research towards the potential connection between these chronic conditions is warranted.

KEY WORDS: Cohort study, Comorbidity, Normal pressure hydrocephalus, Schizophrenia, Outcome, Prevalence

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Idiopathic normal pressure hydrocephalus (iNPH) is a progressive and potentially treatable neurodegenerative disease affecting elderly people and characterized by gait impairment and ventricular enlargement in computed tomography (CT) or magnetic resonance imaging (MRI) of the brain, while cognitive impairment and urinary incontinence are often present.[1-3] The only available treatment, cerebrospinal fluid (CSF) shunting, alleviates some the symptoms in the majority of those affected.[4,5] Schizophrenia (SCZ) is a serious mental disorder with high heritability characterized by hallucinations, social withdrawal, and cognitive decline.[6] SCZ is also associated with progressive structural brain changes, including the enlargement of lateral ventricles and the reduction of total gray matter volume.[7] In general, the risk of a Finnish person having SCZ in their lifetime is 0.9%;[8] the Eastern Finnish population exhibiting slightly higher 1.1% lifetime prevalence.[9]

iNPH has been associated with different types of psychiatric manifestations,[10-24] ranging from

ABBREVIATIONS: Abeta, amyloid beta; **CSF,** Cerebrospinal fluid; **CT,** computed tomography; **DSM-IV,** Diagnostic and Statistical Manual of Mental Disorders 4th edition; **HPtau,** hyperphosphorylated tau; **ICD-10,** International Statistical Classification of Diseases and Related Health Problems 10th revision; **iNPH,** idiopathic normal pressure hydrocephalus; **iNPHGS,** iNPH Grading Scale; **MMSE,** Mini-Mental State Examination; **MRI,** magnetic resonance imaging; **NPH,** normal pressure hydrocephalus; **SCZ,** Schizophrenia; **sNPH,** secondary normal pressure hydrocephalus.

apathy to psychotic symptoms,[10-23] but SCZ as a comorbid condition has not been previously systematically analyzed; SCZ or psychotic symptoms accompanied by iNPH have been reported infrequently in the literature during the past 4 decades (Table 1),[11,14-24] the majority being case reports.[15-18,21-23] However, the latest prospective study indicated an increased prevalence of iNPH in older patients with SCZ (5/24, 24%) in a highly selected hospital population.[14] The prevalence of psychotic symptoms or SCZ in patients with iNPH has been estimated to be low.[12,16,20,24]

In this study, we aim to determine (1) the prevalence of SCZ among Eastern Finnish population suffering from probable/possible iNPH, and (2) the specific effects of comorbid SCZ on the treatment outcome of CSF shunting.

METHODS

Study Design & Participants

NPH Registry and Tissue Bank

Permission for this research was received from the Research Ethics Board of the local University Hospital, a hospital that geographically provides serves neurosurgery to the Eastern Finnish population of approximately 900 000 inhabitants. The study was conducted according to the Declaration of Helsinki and all patients provided informed consent. People suspected to suffer from iNPH in this geographical area were primarily examined by a neurologist and referred for further neurosurgical investigations if the patients exhibited 1 to 3 symptoms possibly related to NPH (impaired gait, impaired cognition, or urinary continence) together with enlarged brain ventricles disproportionate to the size of the sulci of cerebral convexities (Evans' index > 0.3)[2] in CT or MRI (Figure).

From 1991 until 2010, the NPH protocol included a 24-h intraventricular pressure monitoring and a small right frontal cortical biopsy from all patients with suspected iNPH. In early 2010, a systematic CSF sampling from all patients was included and a 3-step prognostic test protocol was launched. First, a CSF tap test is performed to all patients with suspected iNPH, where at least 20% improvement in gait speed in repeated 10-m tests is considered as a positive result. In the second phase, those with a negative tap test undergo a lumbar infusion test, where pathological findings (such as conductance ≤ 10)[3,25] are considered as a positive result. In the third step, participants with a negative finding in both of the abovementioned tests undergo a 24-h monitoring of intraventricular pressure. Similarly, as of 2010, brain biopsies are only acquired from participants who undergo intraventricular pressure monitoring or the CSF shunt surgery.

Study Population and Study Design

Between January 1991 and February 2017 (26 yr), 892 consecutive patients with suspected iNPH were included to the registry (Figure). Altogether 521 (58%) participants were identified to suffer from probable or possible iNPH and 371 (42%) participants were identified as unlikely to have iNPH (instead having, for example secondary NPH (sNPH)).[1,2] All medical records, prescriptions and comorbidities of probable/possible and unlikely iNPH patients were retrospectively and systematically examined for the diagnosis of SCZ.

TABLE 1. The Results of the Literature Search of the Relevant Studies Focusing on Comorbid iNPH and SCZ or Psychotic Symptoms

Search words used	(Normal pressure hydrocephalus) and ((schizophrenia) or (psychotic))					
Articles found from MEDLINE/Pubmed	30					
Articles included[a]	10					
Study	**Country**	**Study type**	**Number of patients**	**Number of patients with probable or possible iNPH with comorbid SCZ**	**Number of patients with probable or possible iNPH with psychotic symptoms**	**PMID**
Yoshino et al. (2016)[14]	Japan	Prospective survey	21[b]	5 (24%)[b]	5 (24%)[b]	26 555 031
Oliveira et al. (2014)[11]	Brazil	Prospective survey	35	0	7 (20%)	24 964 110
Agrawal et al. (2012)[15]	India	Case report	1	1	1 (100%)	23 372 246
Mishra et al. (2011)[16]	India	Case report	1	0[c]	1 (100%)	21 353 138
Chopra et al. (2002)[17]	India	Case report	1	0	1 (100%)	21 206 886
Pinner et al. (1997)[18]	UK	Case report	1	0	1 (100%)	9 549 596
Mauritzi (1987)[19]	UK	Theoretical paper	0	0	0	3 614 004
Dewan et al. (1985)[20]	USA	Comment	0	0	0	4 041 514
Lying-Tunell (1979)[21]	Sweden	Case report	2	0	2 (100%)	433 632
Price et al. (1977)[22]	USA	Case report	1	0	1 (100%)	830 802

Abbreviations: SCZ, schizophrenia; iNPH, idiopathic normal pressure hydrocephalus.

Legend: [a]All articles were read and those included were as follows: (i) written in english and (ii) had participants suspected of probable or possible iNPH or (iii) contributed to the theoretical background on iNPH and schizophrenia or psychotic symptoms. [b]Study consisted 21 older SCZ patients. [c]Patient was suspected to have secondary NPH.[12]

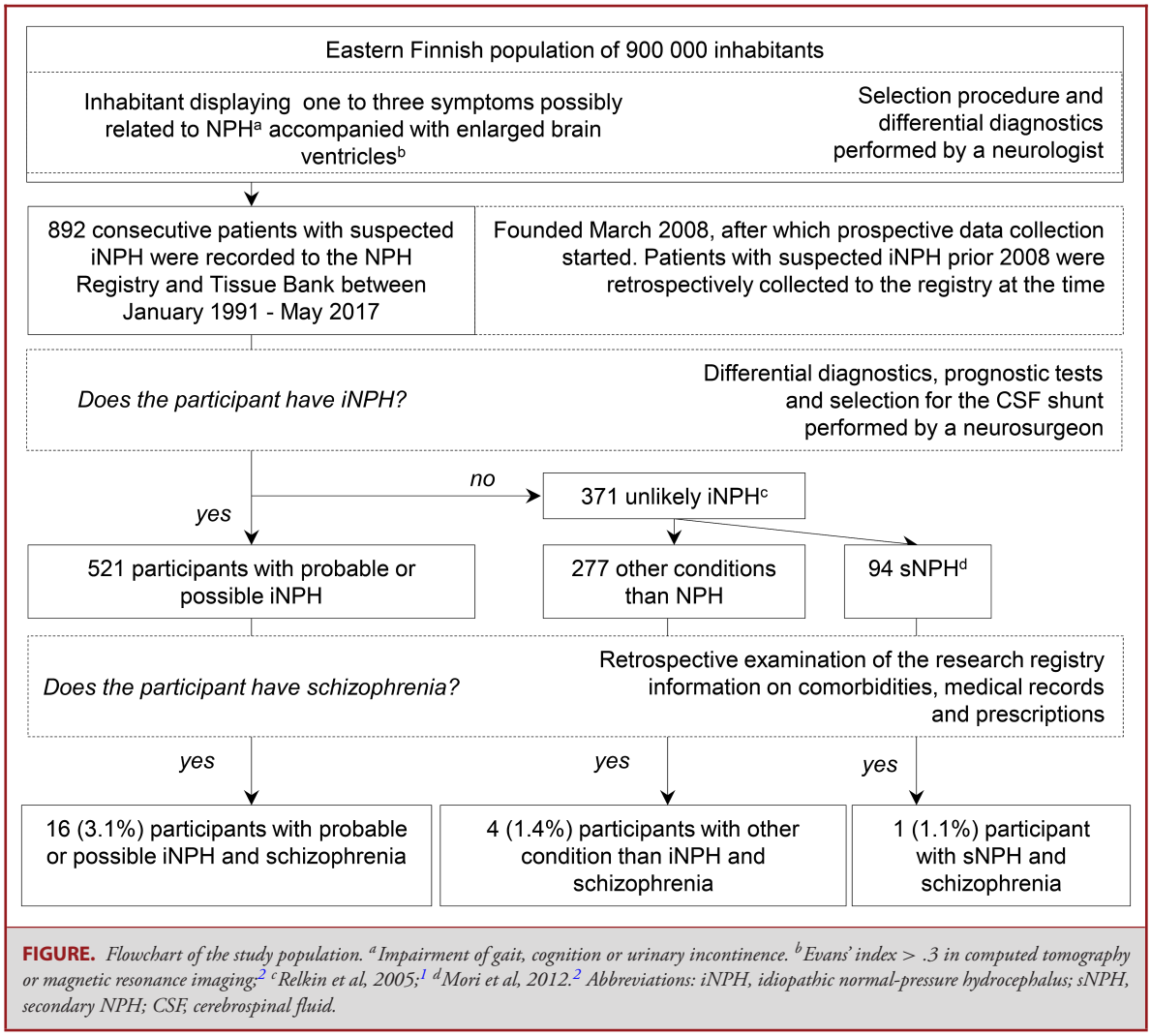

FIGURE. *Flowchart of the study population. [a] Impairment of gait, cognition or urinary incontinence. [b] Evans' index > .3 in computed tomography or magnetic resonance imaging;[2] [c] Relkin et al, 2005;[1] [d] Mori et al, 2012.[2] Abbreviations: iNPH, idiopathic normal-pressure hydrocephalus; sNPH, secondary NPH; CSF, cerebrospinal fluid.*

General Population Control Group

Health 2000 was a general health examination survey based on a nationally representative sample of 8028 people aged 30 yr and older, including a sample of 2157 subjects aged 65 yr or older.[8] Psychotic disorders were screened using information from nationwide health care registers and self-reported symptoms as described in detail elsewhere,[8] and DSM-IV diagnoses were confirmed by using the Structured Clinical Interview for DSM-IV and/or information on psychiatric symptoms from medical records of all lifetime psychiatric treatment contacts.[8] The prevalence of SCZ in the oldest age group has been reported previously.[8] Here, the actual numbers were utilized for a formal statistical comparison of the prevalence of SCZ in patients with iNPH compared to the general population.

Outcome Indicators

To assess the severity of the characterizing symptoms of iNPH, a modified Finnish version of the 12-point iNPH Grading Scale (iNPHGS) was used (Table 2).[26] iNPHGS is a clinician-rated scale to separately estimate the severity of each of the triad symptoms with a scoring based on interviews with the patients or their caregivers and observations by the physician.[26] Lower scores represent less severe symptoms.[26] It has been estimated that even a reduction in the iNPHGS by a single point results in a clinically observable improvement in the patient's condition.[27] Similarly, a clinically verified shunt response was assessed by a neurosurgeon 3 to 12 mo postoperatively at the outpatient clinic.[28] The patient was classified to be nonresponsive to the CSF shunt if no improvement in the core symptoms (gait, cognition, and urinary incontinence) was detected.[28] Cognition was evaluated by using the Mini-Mental State Examination (MMSE).[29] MMSE ranges from 0 to 30, with lower scores indicating a greater cognitive decline.[29]

Frontal Cortical Biopsy

Biopsy needles or forceps were used to obtain one to three cylindrical frontal cortical brain biopsies, of 3 to 7 mm in length and 2 to 5 mm in width, prior the insertion of the ventricular catheter of the CSF shunt (adjacent to the coronal suture of the skull and approximately 3 cm from

TABLE 2. Comparison Between 521 Study Participants With and Without Schizophrenia

Variables	Schizophrenia (n = 16)			no schizophrenia (n = 505)			Test statistics	*P*-value
	Mean or number of participants	SD or %	Number of observations if any missing data	Mean or number of participants	SD or %	number of observations if any missing data		
CSF Shunting surgery								
CSF shunt surgery was performed (yes)	16	100		489	97			>.99[c]
Favorable clinical outcome 3-12 mo postoperatively (yes)	12	75		407	83			.32[c]
Favorable INPHGS outcome (yes)								
3 mo postoperatively	4	40	10	104	48	219		.75[c]
12 mo postoperatively	2	50	4	87	50	173		>.99[c]
Characteristics								
Age (at referral to the neurosurgical department)	65	5.3		73	7.2		$Z = -4.22$	**< .001[a]**
Sex (Female)	8	50		267	53		$\chi^2 = .05$	>.99[b]
History of INPH INPH-related symptoms								
Impairment of gait	13	81		476	94			.07[c]
Urinary incontinence or urge	9	56		374	74			.15[c]
Impaired cognition	11	69		411	81			.20[c]
Full triad	5	31		304	60		$\chi^2 = 5.39$	**.035[b]**
Onset of iNPH-related symptoms			15			499	$\chi^2 = 3.17$	.11[b]
Onset a year or less from the referral	10	66		217	43			
Onset more than a year from the referral	5	34		282	57			
First symptom of iNPH						494		
Impairment of gait or imbalance	9	56		265	54		$\chi^2 = .09$	.81[b]
Cognition impairment	3	19		124	25			.77[c]
Vertigo	2	13		53	11			.68[c]
Urinary incontinence or urge	1	6		27	5			.59[c]
Other	1	6		25	5			.57[c]
Severity of INPH-related symptoms preoperatively								
INPHGS total score (0-12)	6.0	2.1	10	6.2	2.8	247	$Z = -.32$	.75[a]
Cognition impairment (MMSE score, 0-30)	20	4.1	13	22	4.6	429	$Z = -.67$	.10[a]
Comorbidity								
Presence of Abeta or HPtau found in the frontal cortical biopsy	7	44		221	45	490	$\chi^2 = .01$	>.99[b]

ABBREVIATIONS: iNPH, idiopathic normal pressure hydrocephalus; iNPHGS, iNPH Grading Scale; MMSE, Mini-Mental State Examination; CSF, Cerebrospinal fluid.
LEGEND: Statistically significant difference ($P < .05$) is bolded. [a]Mann–Whitney U test; [b]Pearson chi-square test [c]Fisher's exact test.

the midline).[28,30] The presence of hyperphosphorylated tau (HPtau) and amyloid-beta (Abeta) were assessed from all samples by a neuropathologist by using light microscopy (Table 2).[31]

Statistics

The data were analyzed by using the Statistical Package for Social Sciences (SPSS 19 for Windows, Version 19.0. IBM Corp, Armonk, New York). Pearson's Chi-square test or Fisher's exact test was used in multiple comparisons to estimate group differences in nominal variables and the Mann–Whitney *U* test for continuous variables, respectively. The Mann–Whitney *U* test was used due to the nonnormal distribution of continuous variables. To test the difference in the prevalence of SCZ between the studied patients and the general population, the cases of SCZ were weighted by the amount of observations in both populations and compared. All tests for significance were 2-sided, with probabilities of $< .05$ accepted as statistically significant.

RESULTS

Sixteen (3.1%) participants with probable or possible iNPH were identified to have comorbid SCZ, the most common SCZ subtype being residual SCZ (25%; Figure, Table 3). All observed SCZ subtypes, 5-yr occurrences of SCZ, and the prognostic/ancillary tests performed on to patients suffering from SCZ prior to the CSF shunting, are presented in (Table 3). The observed prevalence of comorbid SCZ among iNPH patients was significantly higher compared to the age-weighted control sample set from the general population (3.1% vs 0.9%, absolute risk difference 2.2%; Fisher's exact test, $P < .001$; Table 4).

All participants with SCZ were CSF shunted and 12 (75%) of them had a favorable clinical outcome assessed by a neurosurgeon 3 to 12 mo after the procedure (Table 2). Favorable outcome rates, measured by INPHGS or assessed by a neurosurgeon, did not differ statistically between iNPH patients with

TABLE 3. Characteristics of 16 Participants With Schizophrenia

	Number of subjects with schizophrenia (% of total sample)	Number of participants with iNPH (% of participants with SCZ)
SCZ subtypes (ICD-10)		
Residual schizophrenia (F20.5)	4 (25)	
Paranoid schizophrenia (F20.0)	3 (19)	
Chronic schizophrenia (F20)	2 (13)	
Catatonic schizophrenia (F20.2)	1 (6)	
Hebephrenic schizophrenia (F20.1)	1 (6)	
Schizophrenia, unspecified (F20.9)	1 (6)	
SCZ without subtype specification	4 (25)	
5-yr occurrence of SZC in the NPH registry		
1991-1995	2 (13)	42 (5)
1995-2000	2 (13)	48 (4)
2000-2005	1 (6)	85 (1)
2005-2010	2 (13)	114 (2)
2010-2015	6 (37)	162 (4)
2015	3 (18)	56 (5)
Prognostics and ancillary tests used preliminary to CSF shunt		
CSF tap test	7 (44)	
CSF tap & infusion tests	2 (12)	
ICP monitoring	7 (44)	

ABBREVIATIONS: iNPH, idiopathic normal pressure hydrocephalus; CSF, Cerebrospinal fluid; ICP, Intracranial pressure; SCZ, Schizophrenia; ICD-10, International Statistical Classification of Diseases and Related Health Problems 10th revision.

TABLE 4. Comparison of Prevalence of Schizophrenia Between NPH Registry and a Sample From the General Population

		Population		Comparisons	
		NPH Registry n = 521	Age-weighted[a] Sample of 65 yr olds or older from the general population n = 746 711	Absolute risk difference	Fisher's exact test *P*-value
Schizophrenia	Yes (%)	16 (3.1)	6835 (.9)	2.2%	**< .001**
	No (%)	505 (96.9)	746 711 (99.1)		

ABBREVIATIONS: NPH, Normal pressure hydrocephalus; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders 4th edition.
Legend: [a]Weighted by age using SUDAAN-script to take into account the increased mortality[8] without weighting the general population was the size of 2157 of which 17 people had schizophrenia.[8] In the general population sample,[8] diagnoses of schizophrenia (DSM-IV diagnoses) were confirmed by using the Structured Clinical Interview for DSM-IV and/or information on psychiatric symptoms from the medical records of all lifetime psychiatric treatment contacts,[8] while in our study, the diagnosis of schizophrenia was retrospectively obtained by systematically examining all the medical records, prescriptions and comorbidities of the study population. Statistically significant difference ($P < .05$) is bolded.

and without comorbid SCZ (Table 2). Patients with comorbid SCZ were referred to the neurosurgical department at a significantly younger age than those without SCZ (Mann–Whitney *U*-test, $P < .001$) and exhibited less frequently the triad of core symptoms associated with iNPH (31% vs 60%, Fisher's exact test, $P = .035$; Table 2). Otherwise, the onset and first symptoms, the severity of iNPH-related symptoms and the cognitive impairment of patients with comorbid SCZ were similar to other iNPH patients (Table 2). There was no difference in the prevalence of Alzheimer's disease-related pathology (Abeta or HPtau) in the frontal cortical biopsy between the patient groups (44% vs 45%; Table 2).

DISCUSSION

Interpretation

SCZ was observed to occur 3 times more frequently among the iNPH patients compared to the general aged population in Finland (Table 4), and the number of patients with comorbid SCZ within the NPH registry seems to increase over time (Table 3). The increased awareness of iNPH[24] or the change in the data collection method (Figure) may partly explain the differences in the number of people with SCZ referred to the neurosurgical department and recorded to the registry (Figure and Table 3). As people with SCZ have a higher mortality rate[32] and because

iNPH affects mainly the elderly population,[1-3] the prevalence of comorbid SCZ among the people with iNPH could be underestimated. A recent study[14] hypothesized that the increased prevalence of iNPH in people with SCZ could partly be explained by the vascular risk factors[33] that are also common in patients with iNPH although their exact role in the pathogenesis of iNPH is yet to be determined.[34,35] In 2010, the brief research history of iNPH and SCZ was reviewed in a book chapter on secondary SCZ;[24] two studies[36,37] suggested a common pathology between sNPH and SCZ, and the 2 conditions portrayed similar abnormalities in CSF dynamics in isotope cisternography. However, there was no further replication of these studies.

Identifying iNPH in a person with SCZ is challenging. Even missed diagnoses are possible since ventriculomegaly seen in iNPH could be ignored as the increased volume of ventricles is common in elderly people with SCZ.[24,38] The largely unknown origin of structural brain abnormalities in SCZ has been suggested to possibly reflect the neurodevelopment of SCZ,[38,39] although the progressive enlargement of lateral ventricles can also occur after the onset of SCZ.[7] These structural changes have also been associated with long-term antipsychotic and benzodiazepine use in people with SCZ.[40] Similarly, a part of the clinical appearance of iNPH, the impairment of gait or cognition, could easily be attributed to the side effects of long-standing antipsychotic treatment, or to the normal and highly varying progression/symptomology of SCZ, and thus lead to a missed diagnosis.[14,24] It is important to acknowledge that if an aged person with SCZ exhibits progressive disturbances in gait, cognition, or urinary incontinence that cannot be entirely attributed to the SCZ or its treatment, and if the symptoms are accompanied by ventriculomegaly, iNPH should be considered when sNPH is excluded.[1,2,14,23] In our study, the clinical characteristics of iNPH were nearly equal in the participants with and without comorbid SCZ, but on average, those with SCZ were expressing the classical symptom triad of iNPH less frequently and were referred to the neurosurgical investigations younger than their counterparts (Table 2). A previous study described a similar case of a iNPH patient with comorbid SCZ.[15]It could be hypothesized that coexisting SCZ or its treatment may affect the onset and possibly the progression of iNPH. Otherwise, no further differences were identified in the clinical characteristics.

Comorbid SCZ did not have any effect on the CSF shunt response or the overall treatment outcome between the 2 groups. The observed shunt response rates were in line with the results previously reported in literature.[5] Therefore, iNPH patients suffering from comorbid SCZ should not be left untreated. In our study, due to the limited number of participants with SCZ, the accuracy of different prognostic tests applied prior to the CSF shunting in participants with and without comorbid SCZ and cannot be fully estimated. Based on clinical experience, we suggest that the prognostic tests should be performed in the same way to the patients with and without comorbid SCZ.

Strengths and Limitations

The strengths of this study include large representative population samples from both the people with iNPH and the general aged population. In addition, to the best of our knowledge, ours are the first published findings on the prevalence of SCZ in the iNPH population. Due to the cross-sectional setting in the analyses, we are unable to draw direct conclusions on the causal relationships between iNPH and SCZ. The effect of the CSF shunt on the psychotic symptoms in iNPH patients with comorbid SCZ would have further strengthened the study. The diagnosis of SCZ was retrospectively obtained by systematically examining all the medical records, prescriptions and comorbidities of the study population instead of a psychiatric interview. The participants that were admitted before the year 2008 to the NPH registry were gathered retrospectively at the time. The clinical outcome was not evaluated with INPHGS from all participants. Diagnosis date of SCZ was not captured in our study. However, it was, in all affected, set decades before any suspicion of iNPH. Two different diagnostic guidelines for iNPH exist.[1,2] As symptomatic SCZ patients might be investigated by imaging studies more frequently than older patients without SCZ, an age bias is possible.

CONCLUSION

In summary, SCZ seems to occur 3 times more frequently among iNPH patients as compared to the general aged population in Finland. Still, the treatment outcome is not affected by comorbid SCZ and therefore iNPH patients suffering from comorbid SCZ should not be left untreated. These results merit validation in other populations. In addition, further research towards the possible shared underlying pathological mechanisms of these 2 long-lasting conditions is needed.

Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENT

This study of iNPH in schizophrenia patients performed in Eastern Finland, a reliable health care system environment for such a study, indicates several interesting findings that have remained sidelined until now. In addition to the 3 times higher prevalence of iNPH among schizophrenic patients, the similarity of clinical and radiological phenomena makes the differentiation of the two conditions regarding effect of shunting and prognosis rather difficult. This is the first systematic approach to identify schizophrenic patients that can benefit of shunting (they are usually younger) and the study attempts to assess the outcome that can be expected; in fact, these patients benefitted from shunting at the same rate as general iNPH patients. We believe that with these presented data that we have to consider initial, the relation of iNPH to some of the manifestations of schizophrenia will attract attention and we will improve its understanding.

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