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Normal pressure hydrocephalus (NPH): more about NPH by a physician who is the patient

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ABSTRACT – The incidence of idiopathic normal pressure hydrocephalus (INPH) is seen to be relatively rare, ie about two per million inhabitants per year. Five studies on the prevalence of INPH in elderly patients, from three countries, have been published between 1985 and 2009.[1–5] Prevalence ranged from 0.41% to 2.94% (mean 0.8%), ie slightly less than one per 100 based on samples ranging from 170 to 982 subjects. This surprisingly high percentage was not found in a survey that attempted to identify every person with INPH in a small county in Norway with a population of 219,748. Attempts to identify all patients with INPH overlook many cases. INPH is actually a very common disease and its prevalence increases with age.

KEY WORDS: normal pressure hydrocephalus (NPH)

My first article about normal pressure hydrocephalus (NPH) was published in *Clinical Medicine* in 2007.[1] In that article I described my own case of NPH, which began in about 1992 as a trivial abnormality of gait that was misdiagnosed as Parkinson's disease (PD). Over the next 10 years, during which I was being unsuccessfully treated with dopaminergic drugs for PD, the illness gradually progressed until I could barely walk with a walking frame, had become incontinent of urine and, sometimes, faeces and began to show signs of cognitive loss. In the process of obtaining a motorised wheelchair I was referred to a younger neurologist who recognised that I had run the whole classic course of NPH, a disease of which I had never heard. I had a ventriculoperitoneal shunt (VPS) implanted in 2003 and was miraculously restored virtually to normal. On realising how few practising physicians knew about NPH and how treatable it was I abandoned my area of expertise (hepatology) and dedicated my new life to becoming an expert on NPH and to making physicians and lay people aware of this obscure illness.[2]

Now, in 2010, I consider myself to be such an expert. I have read virtually everything written about the condition. I have had numerous discussions with Salomon Hakim, who first described this syndrome in 1965 and with his son, Carlos, who is the heir apparent to replace his father as the world's titular head of NPH. I have discussed various aspects of NPH with many of the world's foremost experts. I have published a number of articles about NPH in medical journals and lay publications.[1–3] I have lectured and been interviewed on radio, television and in newspapers about the condition. I have participated in major international congresses on hydrocephalus over the past six years, have advised many patients, their families and friends about NPH and its therapy with VPS, and have originated a website (www.nphwatch.net) to answer questions about the condition. I consider Professor Carsten Wikkelsø's invitation to me to deliver the keynote address at Hydrocephalus 2006 (Göteborg, Sweden) to be the seal of approval by the establishment. Finally, I am currently performing studies of NPH, jointly at the Yale and Miller Schools of Medicine of NPH, where I hold appointments as professor of medicine (emeritus) and professor of neurosurgery (voluntary), respectively.

The case history in my first article was written in an unusual manner that was favourably commented upon by a number of readers. The facts about the patient were presented by the author in third person singular and printed in normal type. *They were followed by my comments as the patient in first person singular and printed in italics.*

This article is concerned with two aspects of NPH: first, a misleading oversimplification of terminology about the symptoms and second, the latest estimates of the prevalence of NPH, which reveal it to be a surprisingly common illness.

Oversimplification of the terminology of the symptoms of NPH

Some experts describe the three primary symptoms of NPH as 'gait ataxia, incontinence and dementia'.[4] This oversimplification is inaccurate and misleading and implies that it is a relatively simple disorder rather than a very complex disease. We have good insight into the causes of secondary NPH, but those of idiopathic NPH (INPH) are unknown. The gait in NPH has been described as slow, wide-based, short-stepped, magnetic, frozen and shuffling but it is pathophysiologically a mystery. Besides, it is known that the upper extremities are involved as well.[5] It has also been shown that patients can control their legs much better in a reclining or seated position than when standing.[6] Furthermore, muscle weakness, especially of the quadriceps, as shown by the frequent difficulty that patients with NPH have in climbing stairs and rising from a seated to a standing position. The loss of balance indicates that vestibular function is also involved.[7,8] The posture and muscle stiffness of NPH mimics that of PD.[7,8]

Similarly, urinary incontinence is a misnomer. Frequency and urgency of urination are much more accurate terms than incontinence per se. Incontinence, when it does occur, is usually a late

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symptom that is sometimes the result of the slowness of gait. Besides, it seems to be a sphincteric disease rather than a disorder of the urogenital system. How else can the faecal incontinence be explained?[9]

I had frequency and urgency of urination for several months, which I mistakenly thought was associated with diabetes mellitus because of my family history (both my parents and all three siblings had type 2 diabetes), but there was no glucose in my urine and my fasting blood glucose level was normal. In my case, type 2 diabetes appeared a year or so later along with the polyuria and faecal incontinence and may conceivably be another symptom of NPH.[3] I believe that the triad of symptoms could be more accurately described as 'gait abnormalities', 'urinary frequency, urgency and/or incontinence' and 'mental impairment', as stated by Vanneste et al.[10]

Prevalence of NPH updated: a relatively common syndrome

Although NPH was described almost half a century ago, its prevalence is still uncertain. The prevalence of a disease is defined as the number of cases of an illness at a certain time in a specific place. It is usually presented as per cent or per 100,000. Incidence is the prevalence per unit of time, eg per year. In the beginning, when relatively few physicians knew about the condition, it was considered to be a very rare illness. In 1992, Vanneste *et al* estimated that the incidence of shunt-responsive NPH in Amsterdam to be '…about 2.2 per million per year'.[10] Since Vanneste and colleagues believe that less than half of NPH patients improve after VPS, they must have considered its prevalence to be about four per million. Two years later, Katzman estimated that the total number of cases of NPH in the USA was about 10,000, ie 'one for every neurologist'.[11] Assuming that the population in 1994 was 250,000,000 the prevalence would be one per 25,000, which is still a rare disorder.

Six studies of the prevalence of NPH have been published during the past 25 years (Table 1). In the first of these studies in 1985, Casmiro *et al* reported the frequency of neurologic disorders in the elderly inhabitants of the San Marino, the smallest sovereign state in the world.[12] All inhabitants aged 67, 72, 77, 82 and 87 were invited to be included in the survey. Of 488 volunteers 396 (81%) participated. Each of those with unexplained gait abnormalities or mental impairment had a neurologic examination, a computed tomography (CT) scan of the brain and neuropsychologic testing. The diagnosis of INPH was based on impaired gait, dilatation of the cerebral ventricles, periventricular hypodensities, obliteration of the cerebral sulci at the convexity and 'rounding' of the frontal horns of the lateral ventricles in the absence of cerebral spinal fluid (CSF) obstruction or known causes of secondary NPH, such as intracranial haemorrhage, trauma, cancer surgery or meningitis. Two of the 396 subjects had INPH, a prevalence of 0.005, (one half of one per cent, ie approximately one per 200 subjects). The investigators pointed out that this estimate was a minimal prevalence since they only included subjects who exhibited clinical symptoms of NPH, and some patients with asymptomatic NPH were not included.

The second controlled trial was performed as a door-to-door survey by Trenkwalder *et al* who were studying the prevalence of PD in the inhabitants of two Bavarian villages.[13] They found that among a group of 982 volunteers seven had PD (0.71%) and four had NPH (0.41%). This surprising finding was not commented upon further.

These two surveys appear to closely confirm each other's finding.

Hiraoka *et al* reported the results of their retrospective population study of NPH.[14] They studied 170 randomly selected, elderly subjects (65 years of age or older). They based the diagnosis of INPH on magnetic resonance imaging (MRI) findings of ventricular enlargement and narrowing of the CSF space in the high convexity and high midline areas.[15] The subjects completed a health questionnaire, underwent neurologic examinations, took mini-mental state examinations and clinical dementia rating tests. Their median age was 72.4 years. Thirteen (7.6%) showed ventriculomegaly by Evans Index (>0.3)[16] and five (2.9%) exhibited clinical symptoms of INPH. Thus, eight may have had asymptomatic hydrocephalus and four symptomatic INPH.

Table 1. Prevalence of normal pressure hydrocephalus (NPH): six studies.

First author	Year	Total number of subjects at risk	Number studied (%)	Age ranges	Number of patients with NPH	% of patients with NPH	Location
Casmiro[12]	1985	488	396 (81)	>65	2	0.51	San Marino, Italy
Trenkwalder[13]	1995	1,190	982 (83)	>65	4	0.41	Germany
Hiraoka[14]	2008	2,516	170 (7)	>65	5	2.94	Japan
Tanaka[17]	2009	1,654	561 (30)	61–72	7	1.4	Japan
Iseki[18]	2009	1,142	790 (69)	>65	6	0.76	Japan
Five studies[12-14,17,18]	1985–2009	6,990	2,899 (41)	61–72	24	0.83	San Marino, Italy; Germany; Japan
Brean[19]	2009	219,478	–	–	49 (prob)	0.022	Norway
					58 (poss)	0.026	

GPs = general practitioners; MSc = Master of Science; Pg Cert = postgraduate certificate; Pg Dip = postgraduate diploma; RCP = Royal College of Physicians.

In the fourth study Tanaka *et al* attempted to determine the prevalence of 'possible INPH' among 561 volunteers from Tajiri, Japan, who were 61 to 72 years of age or older[17] and of whom 497 (30%) had undergone MRI. 'Possible INPH' was defined as ventricular enlargement,[16] with 'closing sulci' at the high convexity with dilatation of the Sylvian fissure on MRI, one or more of the cardinal symptoms of NPH and no previous history of any potential cause of secondary NPH. Seven participants satisfied these criteria (1.4%). (Six had cognitive impairment and three had gait abnormalities. None had exhibited urinary incontinence.)

The fifth study is the meticulous analysis of Iseki *et al*.[18] In this investigation all of the residents of Tohoku township aged 61 years (the 'young elderly' group) and of Sagae city aged 70 to 72 (the 'elderly' group) were invited to participate in an investigation in which they responded to a health questionnaire, had a neurologic examination and an MRI of the brain. Of the total 1,142 inhabitants, 790 (69%) accepted the invitation. An MRI diagnosis of 'possible' NPH, which was defined as enlarged ventricles by Evans index[16] and a disproportionate 'narrowing of the subarachnoid space and cortical sulci at the high convexity of the cerebrum' was made in 51 of the 790 subjects (6.5%) of whom 39 had asymptomatic hydrocephalus (5%). Four of the others (0.5%) exhibited gait abnormalities or dementia and eight (1.0%) were asymptomatic. None had urinary symptoms. During an additional period of observation of four to eight years, two of the eight subjects with asymptomatic hydrocephalus developed further dilatation of the ventricles and diffuse brain atrophy. One who had shown no symptoms developed dementia. Six of the 790 (0.8%) had INPH. Thus, asymptomatic hydrocephalus appears to be an earlier stage of symptomatic INPH.

Based on these five population surveys in which a total of 2,988 subjects from three countries were studied, the prevalence of INPH ranged from 0.41 to 2.94% with a mean percentage of 0.76%. Since these estimates are minimal one may generalise that the actual percentage is approximately 1% at age 65. Since the prevalence increases with age (Table 2) it will be even greater when the patients reach their age expectancy, which is currently 80 years and climbing. Thus, well over three million cases will occur in the USA. Such figures are more appropriate for an epidemic than for a rare illness. Furthermore, there are probably as many cases of secondary NPH as there are of INPH.

In the sixth investigation, Brean and Eide used completely different methodology to estimate the prevalence of INPH.[19] Intensive efforts were made to inform the public of their attempt to identify every person with INPH in Vestfeld, Norway (population: 219,748). Local newspapers, radio and television publicised this generally unknown disorder and the attempt to determine its prevalence. Over a 12-month period all healthcare professionals were sent personal letters and were invited to lectures. Lay people were also encouraged to attend. All practitioners, dementia care teams, general and geriatric hospitals, elderly daycare centres, nursing and retirement homes were contacted. Information letters were widely distributed. Referral of all potential patients irrespective of age with a history of three months or more of gait and/or balance problems with impaired cognition and/or urinary symptoms were requested to register or be registered. All registrants were referred to neurological outpatient clinics where a detailed history was obtained, physical examination performed, neuropsychological tests administered and CT or MRI scans performed. Ventriculomegaly was based on Evans Index.[16] Opening CSF pressure was measured at lumbar puncture. The diagnosis of INPH was made in accord with Relkin *et al*'s criteria of 'probable' or 'possible' NPH.[20]

Table 2. Prevalence at various ages.[19]

Age range of patients with NPH	Prevalence per 100,000
50–59 years	3
60–69 years	49
70–90 years	152
>80 years	90
All patients	118

NPH = normal pressure hydrocephalus.

In total, 48 patients fulfilled the criteria for probable INPH, a prevalence of 0.02% (22 per 100,000) (Table 1). (The incidence was 5.5 per 100,000 per year.) Eighteen patients who had had a diagnosis of NPH for which they were shunted were found. Eight had died and were properly excluded, but the 10 who were still alive had also been excluded because clinical details were not available. *I've taken the liberty of including them so that 58 patients had INPH (0.026%).* This prevalence is more than 30 times lower than the mean prevalence as determined by the five population surveys (Table 1). Brean and Eide recognise that the prevalence is much lower than expected and suspect that they did not sufficiently succeed in informing the public about the project.

It is my impression that attempts to identify all the cases of an illness, such as that of Brean and Eide,[19] are doomed to discover fewer cases than actually exist. Many ill, especially those with NPH, or senile patients who may not be in close contact with the real world, might not read newspapers or watch television. Some mailed letters are not received or read. Certainly, those with undiagnosed NPH would be systematically overlooked. Blind, deaf and very ill patients might not be reached by such advertising. Some subjects are too phlegmatic to respond and some are so opposed to organised government of any type that they refuse to cooperate. Some just do not care. Despite the variability of prevalence in the five population studies, which range from 0.4% to almost 3%, I believe that it is safe to generalise that about 1% of the population will develop NPH by the time they reach their age expectancy, which in the USA approaches 80 years.

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