Published in final edited form as:
Alzheimers Dement. 2011 September ; 7(5): 509–513. doi:10.1016/j.jalz.2010.12.008.

Frequency of Alzheimer's Disease Pathology at Autopsy in Patients with Clinical Normal Pressure Hydrocephalus

Danielle Cabral, BA[1], **Thomas G Beach, MD, PhD**[2], **Linda Vedders, BS**[1], **Lucia I Sue, BS**[2], **Sandra Jacobson, MD**[1], **Kent Myers, MD**[1], and **Marwan N Sabbagh, MD**[1]

Danielle Cabral: dcabral@email.arizona.edu; Thomas G Beach: Thomas.Beach@bannerhealth.com; Linda Vedders: Linda.Vedders@bannerhealth.com; Lucia I Sue: Lucia.Sue@bannerhealth.com; Sandra Jacobson: Sandra.Jacobson@bannerhealth.com; Kent Myers: kmyers@midwestern.edu; Marwan N Sabbagh: marwan.sabbagh@bannerhealth.com

[1] The Cleo Roberts Center for Clinical Research, Banner-Sun Health Research Institute, Sun City, AZ, 85351

[2] The Harold Civin Laboratory of Neuropathology, Banner-Sun Health Research Institute, Sun City AZ 85351

Abstract

Background—Normal pressure hydrocephalus (NPH) is considered potentially treatable with the placement of a cerebrospinal fluid (CSF) shunt. Yet, the procedure has had variable success, particularly with respect to improving the cognitive impairment in NPH. The presence of neurologic co-morbidities, particularly Alzheimer's Disease (AD), may contribute to shunt responsiveness. Uncovering the extent to which AD and NPH co-occur has implications for diagnosis and treatment of NPH. Autopsy studies of patients with NPH during life would elucidate the frequency of such co-morbidities.

Methods—We conducted a search of the Sun Health Research Institute Brain Donation Program database between 1/1/1997 and 4/1/09 to identify all cases with neuropathologic evidence of dementia as well as those cases of clinically diagnosed NPH. We reviewed the medical records and brain findings of each NPH case.

Results—Of the 761 cases autopsied over the study interval, 563 cases were found to have neuropathological evidence meeting criteria for a dementing illness. AD was found exclusively in 313/563 (56%) cases with 94/563 cases having a secondary diagnosis of dementia.

Corresponding Author Contact Information: Marwan N. Sabbagh, M.D., Banner-Sun Health Research Institute, The Cleo Roberts Center, 10515 West Santa Fe Drive, Sun City, AZ 85351, Telephone (623) 875-6500, Fax (623) 875-6504.

Disclosures:
Danielle Cabral reports no disclosures.
Dr. Thomas Beach reports no disclosures.
Lucia Sue reports no disclosures.
Linda Vedders reports no disclosures.
Dr. Jacobson reports no disclosures.
Dr. Kent Myers reports no disclosures.
Dr. Marwan Sabbagh
Commercial Entity: Speaking Forest, Eisai, Pfizer, Novartis, Advisory Board Wyeth and Lilly and Amerisciences.
Journal Editor: associate editor for Clinical Neurology News, BMC Neurology, and Journal of Alzheimer's disease
Stock Options: Amerisciences as chairman of the scientific advisory board.
License Fee: For the development of Cognivite Complete for Amerisciences

We identified 9/761 cases with a clinical diagnosis of NPH, all nine cases were among the 563 cases with neuropathology of dementing illness at autopsy, representing 1.6% (9/563). Upon review of brain autopsy reports, 8/9 (89%) cases were found to have AD and 1/9 (11%) had progressive supranuclear palsy. Review of the medical records of the nine NPH cases revealed the following clinical co-morbidities: 5/9 with AD; 1/9 with Parkinson's Disease (PD); 1/9 with Mild Cognitive Impairment (MCI); 1/9 with seizure disorder.

Conclusions—Given the findings of our study, we support the AD-NPH theory and posit that AD is a common pathological co-morbidity in the setting of NPH and may preclude cognitive improvement post-shunt placement. This may have influence on selection of cases for shunting in the future.

Search Terms

normal pressure hydrocephalus; Alzheimer's disease; cerebrospinal fluid shunt; autopsy study; dementia

1. Introduction

Normal pressure hydrocephalus (NPH), first described by Hakim and Adams(1), is characterized by the clinical triad of gait disturbance, cognitive impairment, and urinary incontinence along with radiological evidence of ventriculomegaly out of proportion to cortical atrophy. In practice, clinical presentation is variable, and diagnosis is based on a composite of clinical history, brain imaging, physical findings and physiological measures.(2) The only available treatment for NPH is the placement of a CSF shunt; however, identifying patients most likely to benefit has remained a challenge despite several shunt trials. The recent advent of programmable shunts has brought new attention to NPH, prompting an increased vigilance for NPH and an increasing number of shunting procedures to treat NPH.

It has been theorized that the presence of neurologic co-morbidities in patients with clinical NPH may contribute to shunt responsiveness or lack thereof. Several studies have demonstrated neuropathologic evidence of Alzheimer's disease (AD) in NPH through cortical biopsies taken during shunt placement. The frequency of AD in cortical biopsy has been shown to be greater than that of the general population, suggesting an AD-NPH syndrome. This pathophysiologic relationship has not yet been fully elucidated. One hypothesis is that altered CSF dynamics play a role in the pathologic build-up of beta-amyloid in the brain.(3,4) Uncovering the extent to which AD and NPH co-occur has implications for diagnosis and treatment of NPH.

If an AD-NPH syndrome exists and is at least partly due to altered CSF dynamics, the restoration of proper CSF circulation would seem a reasonable therapeutic approach. Yet, studies have shown that the majority of persons with NPH and concomitant AD do not exhibit cognitive improvement after shunt placement. For these reasons, patient selection for shunt surgery has remained a challenge.

In order to gain insight into the neuropathology of NPH, we identified all NPH cases from our database of deceased donors and reviewed the medical records and autopsy findings of each case. Our analysis of clinical characteristics and neuropathologic diagnoses sheds light on the role of co-morbidities, particularly AD, in NPH.

2. Methods

2.1 Subjects

Study subjects were selected from the Sun Health Research Institute (SHRI) Brain Donation Program. Demographic characteristics of program participants consist primarily of elderly, well-educated, Caucasian, middle and upper income individuals originating commonly from Midwestern US states. The SHRI Brain Donation Program (BDP) has been described in detail elsewhere.(5)

In order to participate in the BDP, subjects sign Institutional Review Board-approved informed consent and undergo medical, neurologic, and neuropsychologic assessments. Outside medical records from primary care physicians, neurologists, and other specialists are also reviewed extensively. At death, prompt brain retrieval and comprehensive brain autopsy are completed by the SHRI neuropathology team.

For this cliniconeuropathologic study, the BDP database was queried to identify all participants with neuropathological evidence of dementing illnesses. Frequencies of underlying cause were compared. Alzheimer's disease was diagnosed using NINCDS-ADRDA criteria,(6) vascular dementia (VaD) using NINDS-AIREN criteria,(7) dementia with Lewy bodies (DLB) according to the Consortium on Dementia with Lewy bodies criteria(8) and frontotemporal dementia (FTD) using the Lund and Manchester Groups criteria.(9)

The database was also queried for all participants with a clinical diagnosis of normal pressure hydrocephalus during life. For our study, those fulfilling a diagnosis of NPH were noted to have gait disturbance and dementia with or without urinary incontinence. Imaging confirmation of dilated ventricles consistent with NPH was present in all cases. These criteria correspond to *probable NPH* as described by current evidence-based guidelines.(2)

Of the identified NPH cases, we reviewed medical records from SHRI assessments as well as those received from outside physicians. Abstracted information included clinical diagnoses, education, CSF shunt status, age at death, and neuropathologic diagnoses.

2.2 Neuropathologic Assessment

All autopsies were performed by a certified neuropathologist at the Sun Health Research Institute. The mean postmortem interval was 2.8 hours. Brain tissue is processed for neuropathological examination in a standardized protocol as previously described.(5) Briefly, paraffin blocks containing brain tissue were cut at 5-μm intervals and stained with hematoxylin-eosin for analysis. Additional paraffin sections containing tissue from the olfactory bulb, anterior medulla, anterior and midpons, amygdala with adjacent entorhinal and transentorhinal areas, middle frontal gyrus, middle temporal gyrus and inferior parietal lobule were stained for immunohistochemical analysis of α-synuclein to identify Lewy bodies and Lewy-related neurites, using a method previously described.(10,11) The diagnosis of AD was made when there was a clinical history of dementia and the histopathological assessment of the brain was consistent with the categories of “intermediate” or “high” as established by criteria outlined in a joint publication by the National Institute on Aging and the Reagan Institute (NIA-Reagan).(12)

3. Results

Of the 761 cases autopsied between 1/1/1997 and 4/1/09, 563 cases were found to have neuropathologic evidence of dementing illnesses at autopsy, and the remaining 198 cases were without evidence of a neurodegenerative disease pathologically. Of these 563 cases,

various etiologies were identified including Alzheimer's disease, vascular dementia, Lewy Body Dementia, frontotemporal dementia, or lastly, a category of other dementing illness, including progressive supranuclear palsy, multiple sclerosis, Huntington's disease, and corticobasal degeneration. AD was found exclusively in 313/563 (56%) cases with an additional 94 cases having a secondary diagnosis of dementia in addition to AD pathology. These secondary diagnoses included 41/94 with AD and VaD, 49/94 with AD and DLB, and 4 with AD and other dementing illness (see list above). The remaining 156 cases had a sole neuropathologic cause of the above listed dementia etiologies with the following frequencies: 16/563 (2.7%) VaD; 8/563 (1.4%) DLB; 3/563 (0.5%) FTD; and 70/563 (12%) Dementia NOS.

The database yielded 9/761 cases with clinically-confirmed NPH during life. As such, all nine NPH cases demonstrated clinical cognitive impairment. At autopsy, the nine NPH cases were found to have neuropathologic evidence of dementing illness, which represents 1.6% (9/563) of all neuropathologic dementia cases. Of the 198 donors without evidence of a neurodegenerative disease at autopsy, there were zero cases of clinical NPH during life. The medical records of the nine cases were reviewed. Clinical diagnoses, age at death, education, and neuropathologic diagnoses are shown in Table 1. The following clinical co-morbidities were present: 5/9 with AD; 1/9 with Parkinson's Disease (PD); 1/9 with Mild Cognitive Impairment (MCI); 1/9 with seizure disorder. Upon review of brain autopsy reports, 8/9 (89%) cases were found to AD and 1/9 (11%) had progressive supranuclear palsy. Concomitant neuropathologic diagnoses included: 1/9 DLB; 3/9 cerebral white matter rarefaction; 2/9 argyrophilic grains, mesial lobe.

4. Discussion

In this clinico-neuropathologic study of a cohort of brain donors with clinically-confirmed NPH during life, our most striking finding at autopsy is that 8 of 9 (89%) cases met NIA-Reagan criteria of AD. (12) We also found that NPH occurred in 1.6% (9/563) of all subjects with dementia in our database of deceased donors, corresponding to previous epidemiologic reports of NPH in 0-3% of dementia cases.(13,14) In our series, NPH rarely exists in the absence of other neurodegenerative conditions and does not commonly appear to be a sole contributor to a dementia process.

There has been ongoing debate as to the validity of NPH as a true diagnosis, thereby calling into question the benefits of shunting, in light of the risks.(15) Shunt trials have consistently demonstrated greater success in treating the gait disturbance and incontinence of NPH with minimal improvement in cognition. Silverberg posits that the dementia in NPH is of multifactorial etiology and the lack of response may represent, in part, fixed tissue damage. (16)

Prior research has investigated the prevalence of AD pathology in NPH. Several studies analyzed cortical biopsies taken from subjects with NPH during shunt surgery, and reported AD pathology in 18-75% of cases.(17-21) The variability may be partly attributable to NPH clinical diagnostic criteria. By current evidence-based guidelines, a diagnosis of probable NPH requires presence of gait disturbance along with cognitive impairment and/or urinary incontinence.(2) The guidelines also further distinguish the characteristic findings of cognitive impairment in NPH versus AD, which is an important distinction for diagnosis and treatment purposes. Nonetheless, in practice, it can be challenging to fit the clinical symptoms into an NPH or AD category. Perhaps when dementia is the primary symptom at clinical presentation, the likelihood of AD is greater. In these cases, shunting may have less robust clinical response, as evidenced by a recent double-blind, randomized, placebo-

controlled study of 251 subjects with probable AD which found no benefit to low-flow CSF shunting in AD subjects.(22)

Our study has several strengths. Comprehensive neuropathologic examinations were important to confirm post-mortem diagnoses. Additionally, we were able to identify cases from a large database of clinical and neuropathologic data on deceased persons. This study is also strengthened by the review of detailed medical records from SHRI and from external clinicians.

The small sample size of NPH patients may limit the generalizability of the findings. However, the frequency of NPH in our sample was comparable to epidemiologic reports of NPH in dementia patients. Additionally, the clinical diagnosis of AD in 5/9 NPH cases may confound the analysis. Yet, excluding persons with a clinical diagnosis of AD seems to be less reflective of the general population.

All nine NPH cases in our study demonstrated cognitive impairment at clinical presentation. Some may argue that this could bias the findings, as our sample may reflect the more severe cases of NPH, which are more likely to have neuropathologic co-morbidities, such as AD. That being said, NPH is widely known as “a reversible form of dementia” through placement of a CSF shunt. Based on our autopsy findings and cortical biopsy studies, AD is a prevalent co-morbidity in clinical NPH. Clinicians should have a greater suspicion of the existence of AD in patients with possible NPH and should undertake appropriate clinical assessment prior to consideration of shunt surgery.

It has been proposed that altered CSF dynamics exist in both AD and NPH, and an AD-NPH syndrome may occur as a result of co-existing pathophysiology.(4,23,24) Given the findings of our current study, we support this theory and posit that AD is a common pathological co-morbidity in the setting of NPH. Indeed, NPH as a single entity may be quite rare. This may have influence on selection of cases for shunting in the future. Longitudinal studies of larger samples of NPH cases providing detailed, standardized clinical assessments pre- and post-shunt placement are needed and may further clarify the AD-NPH relationship.

Acknowledgments

Research Support: Grants/contracts from Wyeth, Elan, Baxter, BMS, Medivation, Avid

References

1. Hakim S, Adams R. The special clinical problem of symptomatic hydrocephalus with normal cerebrospinal fluid pressure. Observations on cerebrospinal fluid hydrodynamics. J Neurol Sci. 1965; 2:307–27. [PubMed: 5889177]
2. Relkin N, Marmarou A, Klinge P, Bergsneider M, Black PM. Diagnosing idiopathic normal-pressure hydrocephalus. Neurosurgery. 2005 Sep; 57(3):4–16.
3. Ghersi-Egea JF, Gorevic PD, Ghiso J, Frangione B, Patlak CS, Fenstermacher JD. Fate of cerebrospinal fluid-borne amyloid beta-peptide: Rapid clearance into blood and appreciable accumulation by cerebral arteries. Journal of Neurochemistry. 1996 Aug; 67(2):880–3. [PubMed: 8764620]
4. Silverberg GD, Mayo M, Saul T, Rubenstein E, McGuire D. Alzheimer's disease, normal-pressure hydrocephalus, and senescent changes in CSF circulatory physiology: a hypothesis. Lancet Neurology. 2003 Aug; 2(8):506–11. [PubMed: 12878439]
5. Beach TG, Sue LI, Walker DG, Roher AE, Lue LF, Vedders L, et al. The Sun Health Research Institute Brain Donation Program: Description and experience, 1987-2007. Cell and Tissue Banking. 2008 Sep; 9(3):229–45. [PubMed: 18347928]

6. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group* under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology. 1984; 34:939–44. [PubMed: 6610841]
7. Roman G, Tatemichi T, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. Neurology. 1993; 43(2):250–60. [PubMed: 8094895]
8. McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H, et al. Diagnosis and management of dementia with Lewy bodies - Third report of the DLB consortium. Neurology. 2005 Dec; 65(12):1863–72. [PubMed: 16237129]
9. Brun A, Englund B, Gustafson L, Passant U, Mann DMA, Neary D, et al. Clinical and Neuropathological Criteria for Frontotemporal Dementia. Journal of Neurology Neurosurgery and Psychiatry. 1994 Apr; 57(4):416–8.
10. Beach TG, Adler CH, Lue LF, Sue LI, Bachalakuri J, Henry-Watson J, et al. Unified staging system for Lewy body disorders: correlation with nigrostriatal degeneration, cognitive impairment and motor dysfunction. Acta Neuropathologica. 2009 Jun; 117(6):613–34. [PubMed: 19399512]
11. Beach TG, White CL, Hamilton RL, Duda JE, Iwatsubo T, Dickson DW, et al. Evaluation of alpha-synuclein immunohistochemical methods used by invited experts. Acta Neuropathologica. 2008 Sep; 116(3):277–88. [PubMed: 18626651]
12. Ball M, Braak H, Coleman P, Dickson D, Duyckaerts C, Gambetti P, et al. Consensus recommendations for the postmortem diagnosis of Alzheimer's disease. Neurobiology of Aging. 1997 Jul-Aug; 18(4):S1–S2. [PubMed: 9330978]
13. Clarfield AM. The decreasing prevalence of reversible dementias - An updated meta-analysis. Archives of Internal Medicine. 2003 Oct; 163(18):2219–29. [PubMed: 14557220]
14. Hejl A, Hogh P, Waldemar G. Potentially reversible conditions in 1000 consecutive memory clinic patients. Journal of Neurology Neurosurgery and Psychiatry. 2002 Oct; 73(4):390–4.
15. Vanneste J, Augustijn P, Dirven C, Tan WF, Goedhart ZD. Shunting Normal Pressure Hydrocephalus: Do the benefits outweigh the risks? A multicenter study and literature review. Neurology. 1992 Jan; 42(1):54–9. [PubMed: 1734324]
16. Silverberg GD. Normal pressure hydrocephalus (NPH): ischaemia, CSF stagnation or both. Brain. 2004 May.127:947–8. [PubMed: 15111447]
17. Del Bigio MR, Cardoso ER, Halliday WC. Neuropathological changes in chronic adult hydrocephalus: Cortical biopsies and autopsy findings. Canadian Journal of Neurological Sciences. 1997 May; 24(2):121–6. [PubMed: 9164688]
18. Golomb J, Wisoff J, Miller DC, Boksay I, Kluger A, Weiner H, et al. Alzheimer's disease comorbidity in normal pressure hydrocephalus: prevalence and shunt response. Journal of Neurology Neurosurgery and Psychiatry. 2000 Jun; 68(6):778–81.
19. Savolainen S, Paljarvi L, Vapalahti M. Prevalence of Alzheimer's disease in patients investigated for presumed normal pressure hydrocephalus: A clinical and neuropathological study. Acta Neurochirurgica. 1999; 141(8):849–53. [PubMed: 10536721]
20. Leinonen V, Alafuzoff I, Aalto S, Suotunen T, Savolainen S, Nagren K, et al. Assessment of beta-amyloid in a frontal cortical brain biopsy specimen and by positron emission tomography with carbon 11-labeled Pittsburgh Compound B. Archives of Neurology. 2008 Oct; 65(10):1304–9. [PubMed: 18695050]
21. Bech-Azeddine R, Hogh P, Juhler M, Gjerris F, Waldemar G. Idiopathic normal-pressure hydrocephalus: clinical comorbidity correlated with cerebral biopsy findings and outcome of cerebrospinal fluid shunting. Journal of Neurology Neurosurgery and Psychiatry. 2007 Feb; 78(2): 157–61.
22. Silverberg GD, Mayo M, Saul T, Fellmann J, Carvalho J, McGuire D. Continuous CSF drainage in AD - Results of a double-blind, randomized, placebo-controlled study. Neurology. 2008 Jul; 71(3): 202–9. [PubMed: 18525029]
23. Rubenstein E. Relationship of senescence of cerebrospinal fluid circulatory system to dementias of the aged. Lancet. 1998 Jan; 351(9098):283–5. [PubMed: 9457114]

24. Chakravarty A. Unifying concept for Alzheimer's disease, vascular dementia and normal pressure hydrocephalus - a hypothesis. Medical Hypotheses. 2004; 63(5):827–33. [PubMed: 15488655]

Table 1

Clinical and neuropathological information for NPH cases

Case ID	Gender	Education	Comorbidity#1	Comorbidity#2	Received Shunt?	Age at Death	NP Dx1	NP Dx2	NP Dx3	NP Dx4
1	F	16			+	82	AD	Argyrophilic grains, mesial lobe		
2	M	14	AD	Parkinsonism	+	80	AD	Microscopic DLB (sufficient for dx)	Chronic superficial cortical gliosis	
3	M	16	AD		+	79	AD	Cerebral white matter rarefaction	Old cortical microscopic infarct, left middle frontal gyrus	
4	F	15	AD	Parkinsonism	+	82	AD	Microscopic DLB (insufficient for diagnosis)	Argyrophilic grains, mesial lobe	Glial tauopathy, basal ganglia
5	M	14	MCI		+	77	AD	Cerebral white matter rarefaction	Acute right capsular hemorrhage	Old hemorrhagic microscopic infarct
6	M	20	PD	MCI	+	77	PSP	Microscopic changes of AD (insufficient for diagnosis)	Mild bilateral chronic subdural hematoma	
7	M	Not known	Dementia	Seizure disorder	+	94	AD	Chronic inflammatory cell infiltrates		
8	F	Not known	AD		+	95	AD	Microscopic DLB (insufficient for diagnosis)	Cerebral white matter rarefaction	Arachnoid cyst, left parietal lobe
9	F	16	AD		+	91	AD	Microscopic DLB (insufficient for diagnosis)		

AD=Alzheimer's Disease. MCI=mild cognitive impairment. DLB=Dementia with Lewy Bodies. PD=Parkinson's Disease. PSP=progressive supranuclear palsy.