



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

Danielle Cabral BA<sup>1</sup>, Thomas G Beach MD, PhD<sup>2</sup>, Linda Vedders BS<sup>3</sup>, Lucia I Sue BS<sup>4</sup>, Sandra Jacobson MD<sup>3</sup>, Kent Myers MD<sup>3</sup>, Marwan N Sabbagh MD<sup>3</sup>

<sup>1</sup>. University of Arizona College of Medicine, Phoenix, AZ 85044  
<sup>2</sup>. The Harold Civilin Laboratory of Neuropathology, Banner-Sun Health Research Institute, Sun City AZ 85351  
<sup>3</sup>. The Cleo Roberts Center for Clinical Research, Banner-Sun Health Research Institute, Sun City, AZ, 85351

### Introduction

Normal pressure hydrocephalus (NPH), 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, is considered potentially treatable with shunting. Yet, the procedure has had variable success, particularly with respect to improving the cognitive impairment in NPH.

It has been theorized that the presence of neurologic comorbidities in patients with clinical NPH may contribute to shunt responsiveness. Several studies have demonstrated neuropathologic evidence of Alzheimer's disease (AD) in NPH through cortical biopsies taken during shunt placement. Uncovering the extent to which AD and NPH co-occur has implications for diagnosis and treatment of NPH. Autopsy studies of patients with normal pressure hydrocephalus during life would further elucidate the frequency of comorbidities in NPH.

### Methods

#### 1. Subjects

Study subjects were selected from the Sun Health Research Institute Brain Donation Program (BDP). BDP participants sign IRB-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. The BDP database was queried to identify all participants with neuropathological evidence of dementing illnesses as well as for all participants with a clinical diagnosis of normal pressure hydrocephalus. 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. 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. 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 "mild" as established by criteria outlined in a joint publication by the National Institute on Aging and the Reagan Institute (NIA-Reagan).

### Results

Of the 751 cases autopsied over the study interval (1/1/1997 and 4/1/09), 563 cases were found to have post-mortem neuropathologic evidence of dementing illness. AD was found exclusively in 313/563 (56%) cases with 94/563 cases having a secondary diagnosis of dementing illness. The remaining 156 cases had a sole neuropathologic cause with the following frequencies: 16/563 (2.7%) Vascular dementia; 8/563 (1.4%), Lewy Body Dementia; 3/563 (0.5%) Pick's Disease; and 70/563 (12%) Dementia NOS.

We identified 9/563 (1.6%) cases with a clinical diagnosis of NPH. Upon review of brain autopsy reports, 8/9 (89%) cases were found to have AD and 1/9 (11%) had progressive gait/pseudobulbar 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.

B-SHRI Brain Donation Program		Autopsy Data	
Post-mortem Neuropathologic Diagnosis	Count	n=563	%
Alzheimer's Disease	313	56	
AD + secondary dementia diagnosis	94	17	
AD + Vascular Dementia	41		
AD + Lewy Body Dementia	49		
AD + Dementia NOS	4		
Vascular Dementia	16	2.7	
Lewy Body Dementia	8	1.4	
Frontotemporal Dementia	3	0.5	
Other dementing Illness	70	12	

### NPH Cases: Clinical and Post-mortem Neuropathologic Data

Case ID	Gender	Education	Clinical Comorbidities		Received Shunt	Age at Death	Post-mortem Neuropathologic Diagnoses		
			#1	#2			Dx1	Dx2	Dx3
1	F	16			+	82	AD	Argyrophilic grains, mental lobe	
2	M	14	AD	Parkinsonism	+	80	AD	Microscopic DLB	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 dx)	Argyrophilic grains, mental lobe
5	M	14	MCI		+	77	AD	Cerebral white matter rarefaction	Acute right capsular hemorrhage
6	M	20	PD	MCI	+	77	PSP	Microscopic changes of AD (Insufficient for dx)	Mild BL, chronic subdural hematoma
7	M	-	Dementia	Seizure dx	+	94	AD	Chronic inflammatory cell infiltrates	
8	F	-	AD		+	95	AD	Microscopic DLB (Insufficient for dx)	Cerebral white matter rarefaction
9	F	16	AD		+	91	AD	Microscopic DLB (Insufficient for dx)	

### Discussion

Our most striking finding at autopsy is that 8 of 9 (89%) NPH cases met NIA-Reagan criteria of AD.

We also found that NPH occurred in 1.6% (9/563) of all subjects with dementing illnesses in our database of deceased donors, corresponding to previous epidemiologic reports of NPH in 0-3% of dementia cases.

Prior research analyzed cortical biopsies taken from subjects with NPH during shunt surgery, and reported AD pathology in 18-75% of cases.

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.

**Limitations**  
Small sample size of NPH patients  
Clinical diagnosis of AD in 59 NPH cases may limit the generalizability of the findings

### Conclusions

Given the findings of our study, we support the AD-NPH theory and posit that AD is a common pathological comorbidity 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.

### References

- Ball M, Brasck 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(7):81-82.
- Blivenberg GO, Mayo M, Sisay 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):606-611.
- 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.
- Bavoilainen S, Paljärvi L, Vapaatalo 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.
- Bech-Azeddine R, Hogh P, Juhrer M, Giemts F, Waldeimer 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.
- Blivenberg GO, Mayo M, Sisay 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.