Burnett School of Medicine

# Effectiveness of the Evans Index in Differentiating Normal Pressure Hydrocephalus and Alzheimer's Disease

Research Thesis

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Scholarly Pursuit and Thesis

## Abstract

**Research Question:** In people with a diagnosis of normal pressure hydrocephalus (NPH) who had a lumbar puncture or ventriculoperitoneal shunt that yielded resolution of symptoms, is the Evans index an appropriate imaging tool for diagnosis of normal pressure hydrocephalus when trained radiologists evaluate the MRI imaging? Secondly, is the Evans index useful to differentiate NPH from Alzheimer's disease and normal, healthy controls?

**Background, Significance, and Rationale for the Question**: Timely diagnosis of neurodegenerative diseases like Normal Pressure Hydrocephalus (NPH) and Alzheimer's disease (AD) is imperative to treatment. Differentiation of these diseases is difficult as both are characterized by insidious progression of cognitive and ambulatory impairment with ventriculomegaly on brain imaging. The Evans Index (EI) has excellent intra- and inter-observer reliability as a measure of ventriculomegaly in diagnosing NPH. We intend to reinforce the existing body of research demonstrating EI's value in distinguishing NPH from AD.

**Materials and Methods:** This was a retrospective data analysis of MR imaging at a large community hospital in Fort Worth, TX. Reports containing "Normal Pressure Hydrocephalus" or "Alzheimer's Disease" were reviewed and patients with a clinical diagnosis of NPH or AD were included. A total of 18 NPH cases, 23 Alzheimer's cases, and 23 controls with normal MRI reports were included. Cases were deidentified, randomized, and EI was measured by three blinded neuroradiologists. Friedman's Two-way Nonparametric ANOVA was used to analyze group EI values and inter-rater reliability.

**Results:** There were significant differences in EI between the NPH group and the combined AD and Normal group ($p$ value $< 0.0001$). There was no significant difference between the radiologists' measurements ($p$ value $= 0.67$).

**Conclusions**: Our results confirmed EI reliably differentiates NPH versus AD and the inter-rater reliability is sufficient for clinical use to support early intervention. A limitation of this study is that gold standards for diagnosing NPH and AD are based on subjective clinical factors. Future study could use general radiologists who might demonstrate less inter-rater reliability.

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## Research Question

In people with a diagnosis of normal pressure hydrocephalus (NPH) who had a lumbar puncture or ventriculoperitoneal shunt that yielded resolution of symptoms, is the Evans index an appropriate imaging tool for diagnosis of normal pressure hydrocephalus when trained radiologists evaluate the MRI imaging? Secondly, is the Evans index useful to differentiate NPH from Alzheimer's disease and normal, healthy controls?

**Hypothesis:** The Evans index is an appropriate diagnostic tool for differentiating NPH from Alzheimer's disease and quickly identifying normal, healthy controls versus NPH and Alzheimer's patients. If our hypothesis is correct, using the Evans index can help quickly diagnose NPH and support faster treatment to reduce morbidity and mortality and support the current body of evidence suggesting using this criteria in normal practice.

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# Introduction and Significance

## Introduction

Normal Pressure Hydrocephalus (NPH) is a brain condition of inappropriately enlarged cerebral ventricles despite normal pressure when evaluated clinically with a lumbar puncture. The illness was first described in 1965 as a neurocognitive condition characterized by Hakim's Triad of dementia, gait disturbance, and urinary incontinence with no identifiable cause.[1] Many other types of hydrocephalus can occur quickly due to obstruction or physical limitation of CSF flow resulting in increased intracranial pressure, but the term "normal pressure" is used when the increased ventricle size occurs over longer periods as compensation for short-term increases in CSF that are not able to be evaluated using lumbar puncture. Normal pressure hydrocephalus can be further separated into two types: idiopathic (iNPH) with no known cause, and secondary (sNPH), often caused by another pathological process such as subarachnoid hemorrhage, head trauma, brain tumor, or meningitis among others.[2] Computed tomography (CT) or magnetic resonance imaging (MRI) can show ventricular enlargement, periventricular hyperintensities, large sylvian fissures, and narrowed subarachnoid space with no apparent cause that all support a diagnosis of NPH.[3]

## Significance

The dementia, gait disturbance, and urinary incontinence common in NPH can significantly contribute to increased morbidity and mortality as aging patients can no longer function independently as they age and significantly reduces quality of life. A population-based study on the prevalence of idiopathic normal pressure hydrocephalus revealed that approximately 2

million people in Europe (114,394 aged 70–79 years and 1,842,983 aged 80 years or older) and 700,000 in the United States (33,808 aged 70–79 years and 669,178 aged 80 years or older) may suffer from iNPH.[4] However, it is possible that many more individuals are afflicted by this disease because there is wild variability in diagnostic criteria, many physicians do not know how to appropriately recognize and diagnose based on the symptoms, the diagnosis may only be verified using ventriculoperitoneal shunt with resolution of symptoms, and symptoms can return even after treatment.[5] Regardless, treatments including ventriculoperitoneal shunting and serial lumbar punctures can reduce symptoms of NPH and reduce morbidity and mortality even if only in the short term.

Hydrocephalus can also be described in terms of communicating versus non-communicating based on presence of a physical blockage in the ventricles or cerebral aqueducts. In NPH, there is greater pressure not due to a blockage, rather increased outward force on the gyri/sulci due to alterations in the cerebrospinal fluid dynamics explain the pathophysiology. Transient increases in CSF pressure cause ventricular enlargement to compensate and control intracranial pressure. However, the disease often goes undiagnosed due to its late age of onset and similarity to other neurocognitive conditions such as Alzheimer's disease, vascular dementia, Parkinson's Disease, or normal brain atrophy due to aging.[6] Also complicating the diagnosis is that clinicians may attribute the symptoms of iNPH to alternate diagnoses including Alzheimer's disease, dementia with Lewis bodies, or progressive supranuclear palsy.[5]

The mechanism of ventricular enlargement in iNPH is still in debate, but there are two possible explanations.[6] The Windkessel mechanism describes normal arterial stretch during cardiac

systole followed by normal elastic relaxing during diastole. It is proposed that arterial compliance decreases cerebral venous pressure increases to reduce normal pulsatility of the CSF causing backflow. Ventriculomegaly results from the increased pressure on the ventricle walls and increased stress on ependymal cells creating the CSF.

The second mechanism is also related to increased cerebral venous pressure. Although the ependymal cells produce an estimated 500 mL of CSF daily, the normal volume is maintained at roughly 125 mL via the normal drainage of CSF into the arachnoid granulations into the venous system through the superior sagittal sinus.[3] In patients with iNPH, the reabsorption of CSF is reduced due to increased cerebral venous pressure acting against the normal absorption of the CSF through the arachnoid granulations.[6]

**Rationale**

Faster diagnosis of NPH using high-quality imaging such as MRI can speed treatment decisions and reduce morbidity and mortality due to the insidious presentation of symptoms. It can also be useful to rule out other pathology with similar presentation of gait ataxia, urinary incontinence, and dementia. The Evans Index (EI) is a diagnostic tool that may be useful in quickly diagnosing NPH. The EI is calculated as the ratio of the width of the widest part of the frontal horns of the lateral ventricles compared to the maximal internal diameter of the skull at the same level on axial computed tomography (CT) or magnetic resonance imaging (MRI).[7] Measurement of this value can help differentiate isolated increases in ventricle size from the appearance of increased ventricle size due to complete cerebral atrophy associated with other types of dementia. A normal EI is <0.3 and a value >0.3 is necessary for the diagnosis of iNPH.

Clinicians must incorporate the classic symptoms of dementia, gait disturbance, and urinary incontinence into physical exam and also use neuroimaging such as CT and MRI.[8] The following International Guidelines for imaging results can be used in iNPH diagnosis:[9,10]

- Ventricular enlargement with Evans Index >0.3
- Absence of macroscopic obstruction to CSF flow
- At least one of the supporting features:
    - Enlarged temporal horns of the lateral ventricles not entirely due to hippocampus atrophy
    - Callosal angle of 40 degrees or greater
    - Periventricular signal changes on CT and MRI due to altered brain water content (transependymal edema due to increased CSF)
    - Flow void in the sylvian aqueduct or fourth ventricle on MRI

A retrospective research study using fellowship-trained neuroradiologists to evaluate blinded MRI images after clinical diagnosis of NPH was suggested to elucidate the sensitivity/specificity and likelihood ratio of using EI in differentiating NPH from Alzheimer's disease. The electronic health record utilized by the JPS healthcare network provided access to a large patient population with brain imaging that to assess the utility of EI as diagnostic criteria for NPH. Incorporating multiple trained neuroradiologists using the same data set of images allowed us to evaluate interrater reliability when using the EI.

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## Materials and Methods

### Patients

We performed a retrospective assessment of MRI reports gathered between 2019 and 2022 from the John Peter Smith Health Network (JPS) electronic medical record comparing three different populations: those with known diagnosis and imaging of NPH compared to both those with known diagnosis and imaging of AD and normal, healthy control patients. MRI Brain reports from various (JPS) hospital network facilities in Fort Worth, Texas which contained the words “normal pressure hydrocephalus” were included in initial review and patient medical record review was completed to ensure a clinical diagnosis of NPH. Any MRI reports including the terms “Alzheimer’s disease, global cerebral atrophy, temporal lobe atrophy, or temporoparietal atrophy” were included in the record review and patients with clinical diagnoses of Alzheimer’s disease were added to the study population. The search identified 139 patients. A total of 75 patients were then excluded for not having a clinical diagnosis of either NPH (n = 29) or AD (n = 46) to support the suggestive imaging findings. A total of 41 subjects met inclusion criteria after image screening and electronic health record review (n = 18 NPH, n = 23 AD). A total of 23 normal controls of adults >18 years of age with brain MRI and no discernible pathology were gathered for a total of 64 patients.

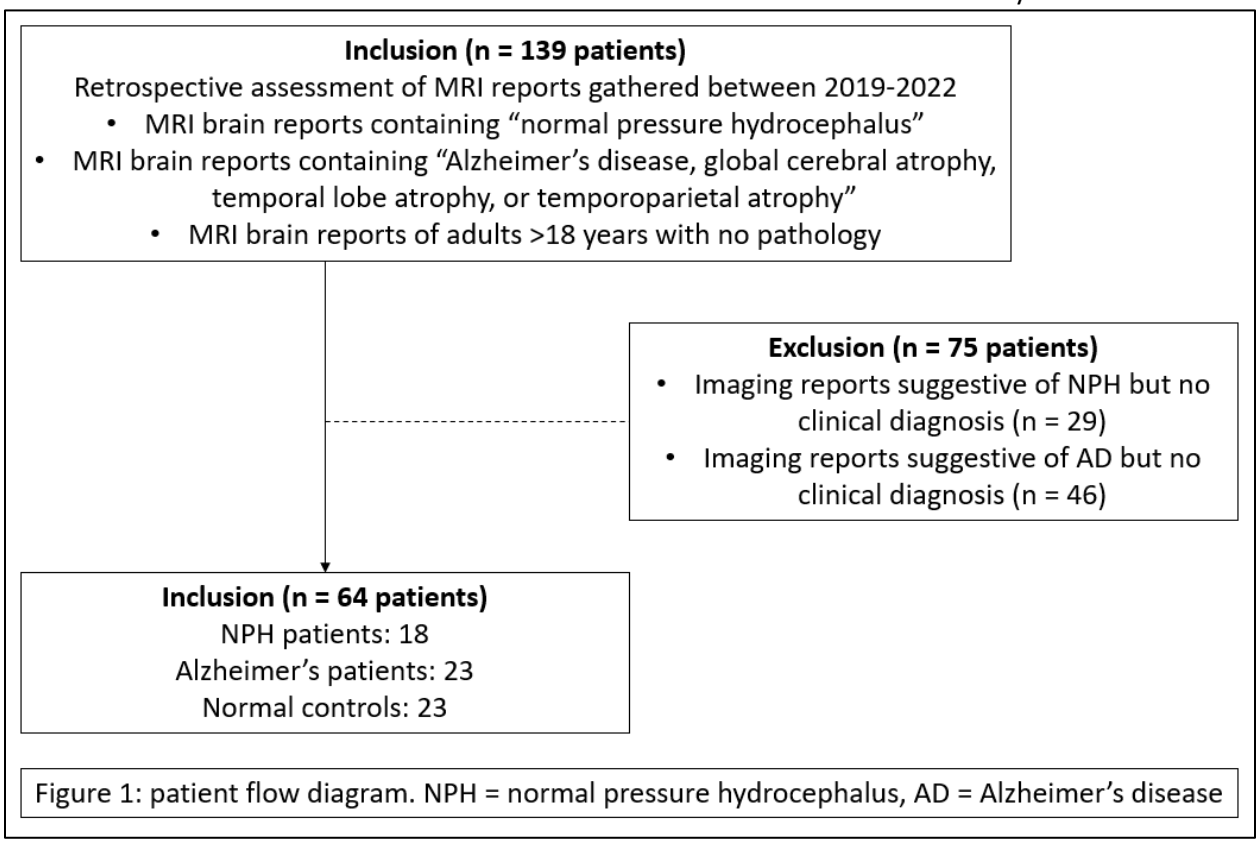


Figure 1: patient flow diagram. NPH = normal pressure hydrocephalus, AD = Alzheimer's disease

**Image Acquisition**

Routine MR sequences of the brain were utilized. Images were deidentified, randomized, and collected in a single list of images to be reviewed using a picture archiving and communication system (PACS) commonly used in clinical radiology practice. Three neuroradiology fellowship trained radiologists, each with greater than ten year's experience, were blinded to the patients' histories, diagnoses, and previous imaging, independently reviewed the images, measured the EI, and diagnosed each patient as either NPH, AD, or normal. The EI and diagnosis for each patient was collected.

**Image Interpretation**

The EI is a simple measurement used in NPH diagnosis and is a validated tool for assessing the presence of ventriculomegaly.15 As demonstrated in Figure 1 on a patient with NPH, the EI is measured as the width of the widest part of the frontal horns of the lateral ventricles compared to the maximal internal diameter of the skull at the same level on axial imaging. Radiologists measured the EI on axial imaging at the widest visible slice of the frontal horns. Figure 2 demonstrates the EI on a patient with AD and Figure 3 demonstrates the same measurement technique on a normal patient.

**Statistical Analysis**

64 subjects who were either normal, diagnosed with NPH, or were diagnosed with AD had their EI measured by three radiologists. A Friedman two-way repeated measure analysis of variance by ranks was performed to compare the repeatedly defined EI for each patient by their brain status. Friedman tests were performed to test differences across all three brain statuses; again to test differences combining normal and NPH against patients with AD; and a third time to test differences combining normal and AD against NPH.

## Results

**Table 1** provides an overview of the three-level disease status, and repeated radiologist EI measurements shown in median and interquartile range (IQR). In patients with known AD, radiologist 1 measured a median EI of 0.27 (IQR 0.26-0.3), radiologist 2 measured a median EI of 0.28 (IQR 0.26-0.29), and radiologist 3 measured a median EI of 0.28 (IQR 0.26-0.29). In patients with known NPH, radiologist 1 measured a median EI of 0.35 (IQR 0.34-0.38), radiologist 2 measured a median EI of 0.36 (IQR 0.34-0.39), and radiologist 3 measured a median EI of 0.355 (IQR 0.33-0.37). In normal controls, radiologist 1 measured a median EI of 0.25 (IQR 0.25-0.26), radiologist 2 measured a median EI of 0.26 (IQR 0.25-0.27), and radiologist 3 measured a median EI of 0.26 (IQR 0.25-0.27). There was no statistically significant difference in how each radiologist measured the EI, regardless of brain status ($p = 0.64$). However, there were statistically significant differences in EI values between NPH, AD, and normal patients ($p = 0.04$). The two-level brain status comparing EI values of the combined normal and AD patients versus NPH patients is detailed in **Table 2.** In patients with known NPH, radiologist 1 measured a median EI of 0.35 (IQR 0.34-0.38), radiologist 2 measured a median EI of 0.36 (IQR 0.34-0.39), and radiologist 3 measured a median EI of 0.36 (IQR 0.33-0.37). In the combined normal and AD patients, radiologist 1 measured a median EI of 0.26 (IQR 0.25-0.28), radiologist 2 measured a median EI of 0.27 (IQR 0.25-0.28), and radiologist 3 measured a median EI of 0.27 (IQR 0.25-0.28). There was again no significant difference in how each radiologist measured EI, regardless of disease status ($p = 0.67$). And again, there were significant differences in EI values between those with NPH and the combined group of normal and AD patients ($P < 0.001$).

**Table 1.** Three Level Patient Status Comparison of Evan's Index Across Three Radiologist

| Patient Status | Radiologist | N | Median Evans Index (IQR) |
|---|---|---|---|
| **Alzheimer** | 1 | 23 | 0.27 (0.26 to 0.3) |
| | 2 | 23 | 0.28 (0.26 to 0.29) |

| | | | |
|---|---|---|---|
| | 3 | 23 | 0.28 (0.26 to 0.29) |
| **Normal** | 1 | 23 | 0.25 (0.25 to 0.26) |
| | 2 | 23 | 0.26 (0.25 to 0.27) |
| | 3 | 23 | 0.26 (0.25 to 0.27) |
| **Normal Pressure Hydrocephalus** | 1 | 18 | 0.35 (0.34 to 0.38) |
| | 2 | 18 | 0.36 (0.34 to 0.39) |
| | 3 | 18 | 0.355 (0.33 to 0.37) |
| **Friedman's Two-way Nonparametric ANOVA** | | | |
| Patient Status | | | p = 0.0444 |
| Radiologist | | | p = 0.6430 |

**Table 2.** Two Level Patient Status Comparison of Evan's Index Across Three Radiologist

| **Patient Status** | **Radiologist** | **N** | **Median Evans Index (IQR)** |
|---|---|---|---|
| **Normal Pressure Hydrocephalus** | 1 | 18 | 0.35 (0.34 to 0.38) |
| | 2 | 18 | 0.36 (0.34 to 0.39) |
| | 3 | 18 | 0.36 (0.33 to 0.37) |
| **Normal + Alzheimer** | 1 | 46 | 0.26 (0.25 to 0.28) |
| | 2 | 46 | 0.27 (0.25 to 0.28) |
| | 3 | 46 | 0.27 (0.25 to 0.28) |
| **Friedman's Two-way Nonparametric ANOVA** | | | |
| Patient Status | | | p < 0.0001 |
| Radiologist | | | p = 0.6731 |

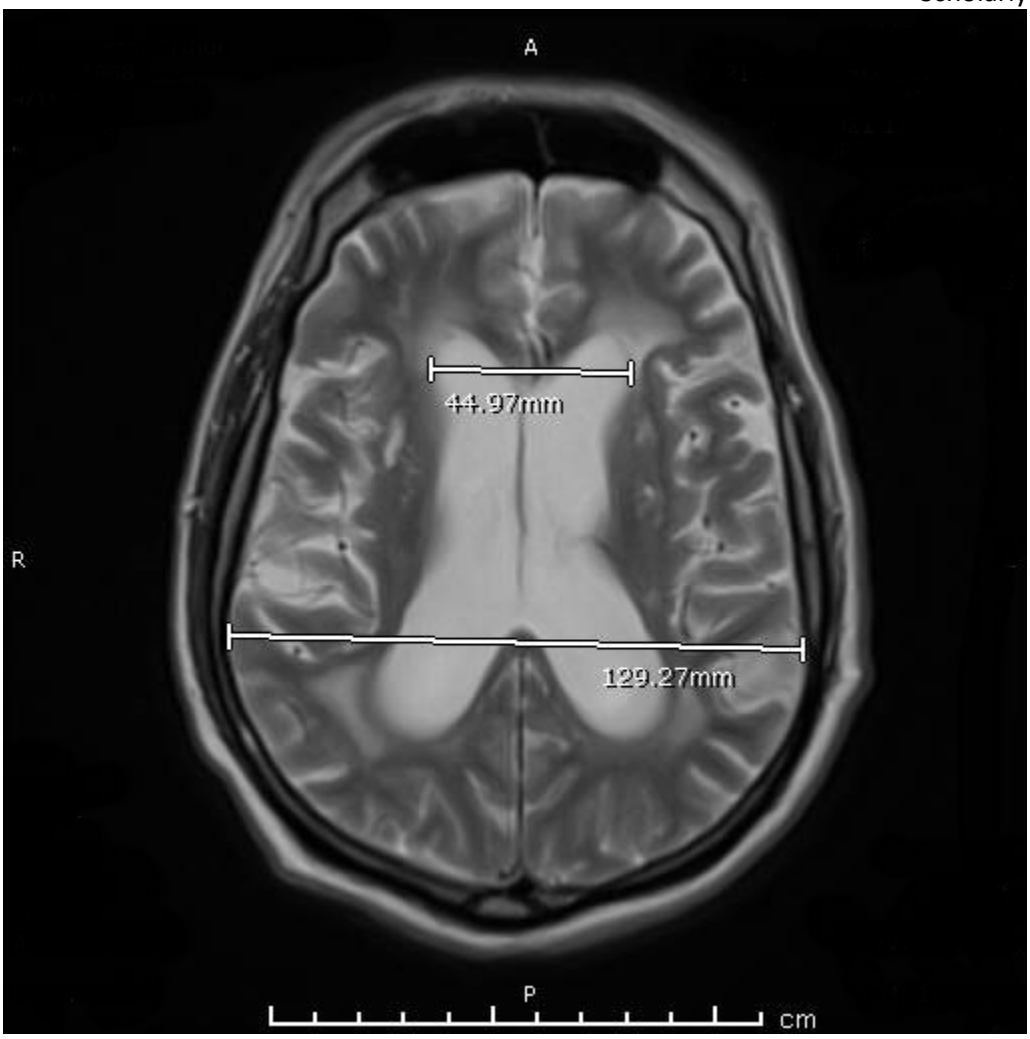


**Figure 1. Example measurement of Evans Index in a patient with NPH (EI = 0.35)**

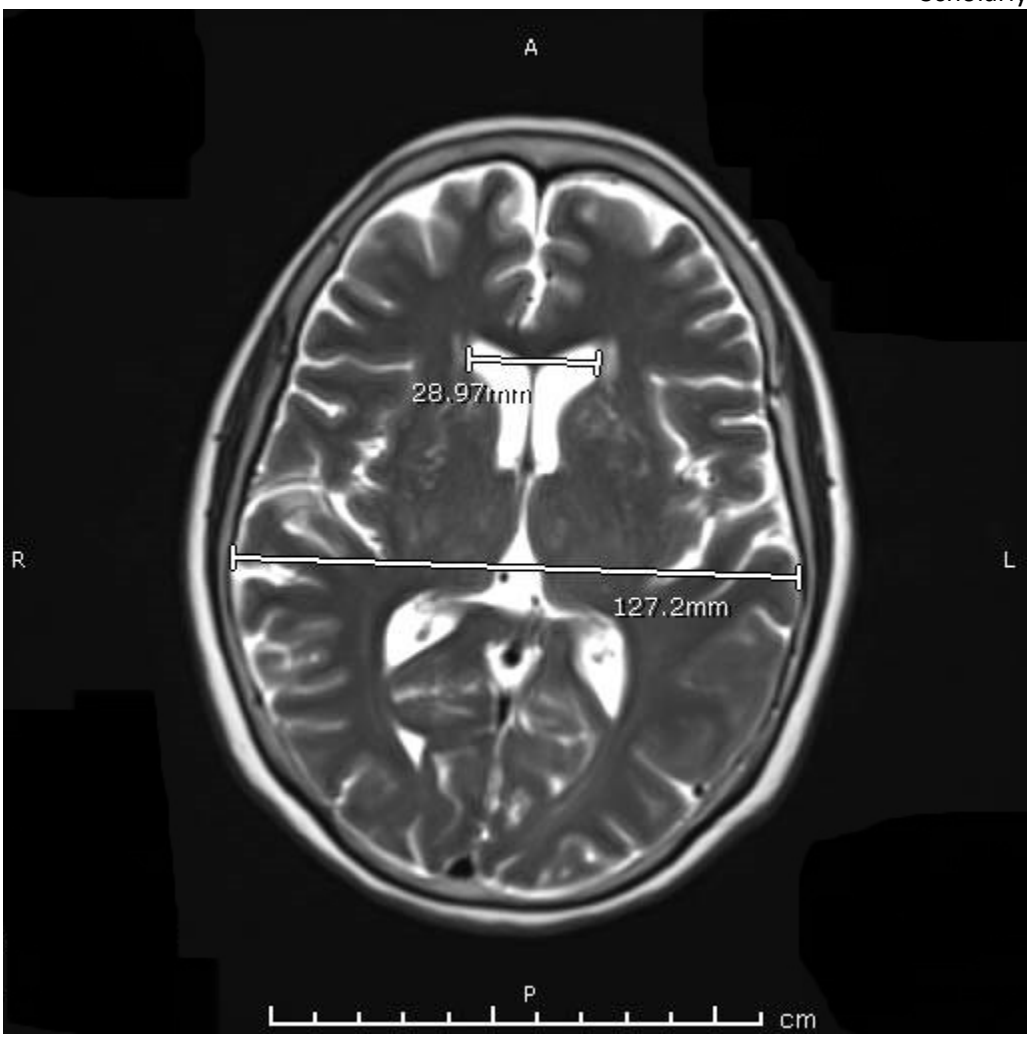


**Figure 2. Example measurement of Evans Index in a patient with AD (EI = 0.23)**

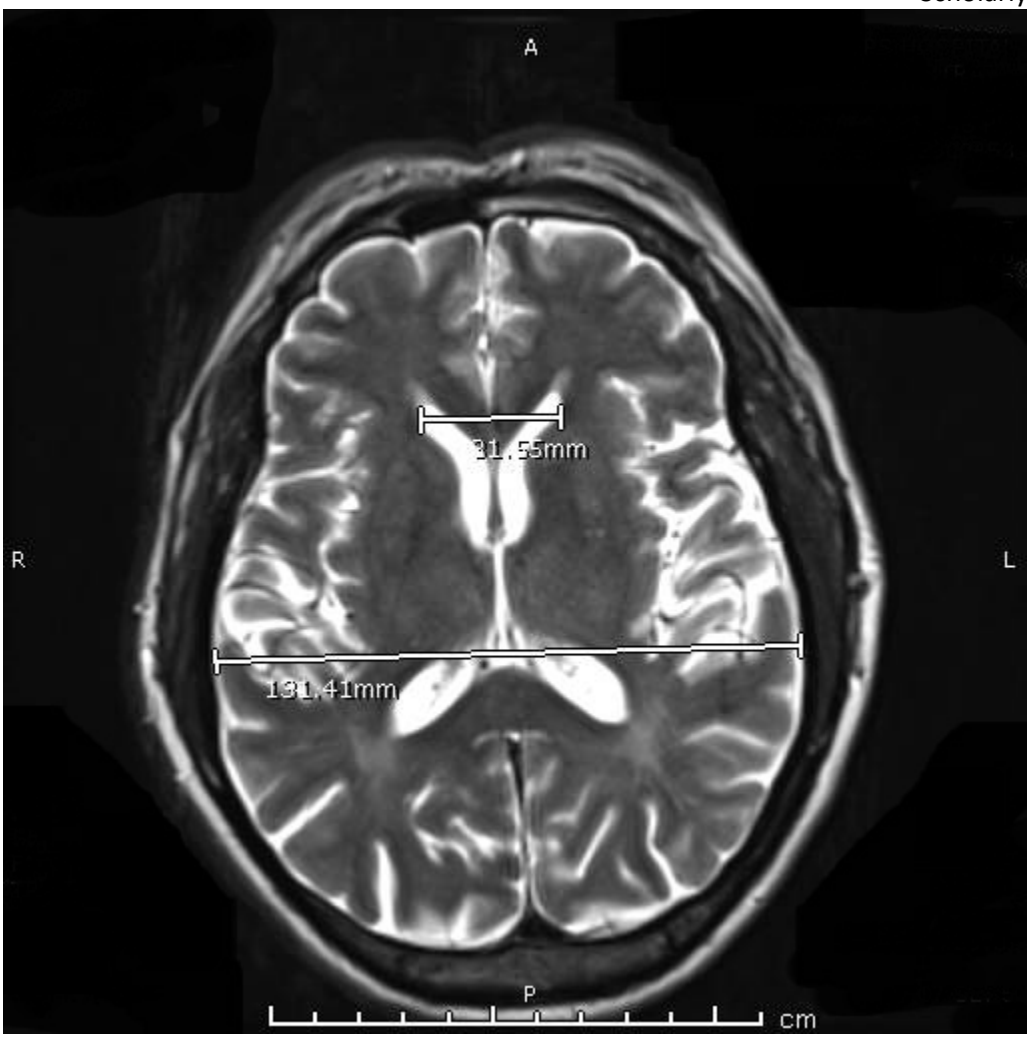


**Figure 3. Example measurement of Evans Index in a normal patient (EI = 0.24)**

## Discussion/Innovation

This study shows that measuring EI alone can accurately differentiate NPH from AD and different radiologists can reliably measure EI. As clinical assessment alone may be insufficient for differentiating NPH [11], incorporating EI into clinical practice has potential for reducing morbidity and mortality in patients suffering symptoms of dementia and support early trial of therapeutic CSF drainage by lumbar puncture. Other, more complex measurements of ventricular size, including ventricular structure analysis with volumetric tissue segmentation, may also be effective; however, this analysis requires additional software and takes significant time to perform [12]. Using EI can increase speed and efficiency of identifying ventricular enlargement patterns in NPH.

Miskin et al. analyzed the effectiveness of EI and another measurement, the callosal angle, compared to volumetric measurement of patients with NPH, AD, and normal controls [12]. That research found the EI had a sensitivity and specificity of 71.3% and 86.7%, respectively and the callosal angle sensitivity and specificity were 87.0% and 89.5%, respectively [12]. When comparing the ventricular volumes of NPH to AD or normal controls, NPH patients had statistically larger ventricular volume ($P < .01$); however, there was no difference in ventricular volume between AD and normal controls ($P < .072$). This finding also supports the use of EI in differentiating NPH from AD or normal controls [12]. A meta-analysis by Park et al. discovered the sensitivity and specificity of the EI in diagnosing NPH was 96% (95% CI, 47-100%) and 83% (95% CI, 77-88%), respectively with an area under the ROC curve of 0.87 (95% CI, 0.84-0.90), again supporting the use of EI in identifying significant ventricular enlargement [13]. When comparing between three radiologists with varying years of experience, Miskin et al. showed an intraclass correlation coefficient (ICC) of 0.81 (95% CI 0.73-0.87). Also supporting its use, EI can be measured on an axial image at the widest view of the frontal horns, a typical image available in almost all routine exams.

The callosal angle has also been proposed as a useful clinical tool in diagnosing NPH; however, its utility remains limited as it requires a specific sequence or reconstruction that is not typically obtained in routine practice [14]. Other research suggests using additional complex measurements of EI in various dimensions [12,15]. Zhou and Xia suggest measuring in the z-axis, called the z-EI, because it has been shown to directly change with increasing ventricular size as the disease progresses [15]. In practice, many patients do not receive serial MRI and using a quick, simple to measure ratio such as EI is equally useful for diagnosis from a single image.

Limitations of this study include the small sample size and the fact we did not have the appropriate number of patients from our initial power analysis. Increasing the initial case screening to imaging acquired before 2019 would likely increase number of NPH, AD, and control cases.

In summary, this study shows that measuring EI alone can accurately differentiate NPH from AD and that EI can be reliably measured by different radiologists. Using only the traditional measurement of EI with a cutoff of >0.3 is sufficient for differentiating NPH from AD and normal controls. There is a high degree of agreement between radiologists when measuring the EI and when identifying NPH, AD, and normal cases on routine brain MRI sequences. Using EI is fast, reliable, and accurate for differentiation of NPH and AD to aid in faster treatment decisions.

## Future Directions

A more comprehensive study, including additional measurements such as the callosal angle and EI measured in three dimensions (traditional x-EI as well as z-EI and y-EI), comparing inter-operator reliability would be helpful, as there could be significant variability between other measurements [16]. To further increase the body of knowledge regarding NPH measurements, a prospective study could enroll patients with suspected NPH based on clinical features and imaging, use multiple measurements (various EI views, callosal angle, and volumetric analysis), and then perform serial measurements after lumbar puncture or shunt placement to assess how these measurements change following treatment.

## Conclusions

This study shows that measuring EI alone can accurately differentiate NPH from Alzheimer's disease and that EI can be reliably measured by different radiologists. Using only the traditional measurement of EI with a cutoff of >0.3 is sufficient for differentiating NPH from AD and normal controls. There is a high degree of agreement between radiologists when measuring the EI and when identifying NPH, AD, and normal cases on brain MRI. Using EI is fast, reliable, and accurate for differentiation of NPH and AD to aid in faster treatment decisions.

## Compliance

Our institutional review board exempted this HIPAA-compliant, retrospective study and waived the requirement to obtain informed consent.

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