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Research Article

Novel Brain Linear Measurements to Differentiate between Alzheimer Disease and Normal Pressure Hydrocephalus

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Abstract

Background: An Evans' index (EI) greater than 0.3 has been associated with a diagnosis of idiopathic normal pressure hydrocephalus (iNPH). However, ventricular enlargement is also present in Alzheimer's disease (AD) in the elderly. To assess the differences between ventricular enlargement in AD and iNPH, we developed a geometric model that incorporated different linear brain measurements and compared it with EI.

Materials and Methods: Different ventricular linear measurements were obtained from 124 brain CT scans of normal participants, AD and iNPH patients. We developed a geometric model that yielded a linear measurement proportional to the skull shape.

The maximum frontal horn distance was divided by this new tool and compared with EI to identify a cutoff point that can allow radiological differentiation between AD and iNPH.

Results: The area under the receiver operating characteristic curve (ROC) when EI was used was 0.803, and the corresponding value with the geometric model (VW_N) was 0.802, i.e. almost identical. The cutoff EI to differentiate between AD and iNPH was 0.36, and the cutoff VW_N to distinguish between AD and iNPH was 1.6.

Conclusion: We show that our novel geometrical method is similar to EI for identifying AD and iNPH. Further research and validation of other ventriculomegaly pathologies are required to increase the usage of the geometrical method. Different patterns of ventricular dilatation with size differences in the dilated frontal ventricular horn are observed in AD and iNPH; linear brain measurements can characterize these differences.

Keywords: Normal Pressure Hydrocephalus; MRI; Dementia; Alzheimer Disease

Abbreviations

AD: Alzheimer Disease; EI: Evans' Index; iNPH: Idiopathic Normal Pressure Hydrocephalus

Introduction

Normal pressure hydrocephalus (NPH) is a complex syndrome associated with ventricular enlargement. Idiopathic NPH (iNPH) should be differentiated from other dementias such as Alzheimer's disease (AD), especially in the elderly. This distinction is very important since iNPH, unlike AD, can be significantly improved by implanting a CSF diversion. Nevertheless, differentiation of these two conditions can be challenging, and neuroimaging is one of the supplementary diagnostic tools along with clinical evaluations to distinguish between the two pathologies. Although both pathologies

show ventricular dilatation, they have different pathophysiologies, with atrophy of the hippocampus predominating in AD and the consequent dilatation of the parahippocampal fissure [1].

Although the SINPHONI [2] study suggests that an enlarged subarachnoid space along with ventriculomegaly is a feature of iNPH, the underlying physiopathology of the condition remains misunderstood, and in the case of iNPH, ventricular enlargement is not entirely related to brain atrophy [3,4]. In this context, EI remains a useful initial radiological tool to assess ventricular enlargement and is well supported by international guidelines [5]; it is considered a hallmark of hydrocephalus.

However, despite the differences in the pathophysiology and ventricular morphology of iNPH and AD, EI has not been used to identify a cutoff value that can distinguish the two pathologies. In the present study, we aimed to determine whether EI or related brain linear measurements can distinguish between iNPH and AD. To this end, we attempted to develop a geometric model that is proportional to the cranial shape and identify differences in ventricular size between AD and iNPH.

Materials and Methods

Study population

We conducted a retrospective study of 124 cases collected from the neuroscience department at King Faisal Specialist Hospital and Research Center in Riyadh and Jeddah branch, Saudi Arabia. The patients presented to the department from January 2000 to December 2018. Since one of the main objectives of the study was to study the elderly population, all selected cases involved patients over 65 years of age, thus avoiding the bias caused by atypical cases in younger patients. Cases demonstrating a history of head trauma, stroke, nervous system infections, brain hemorrhage, secondary causes of hydrocephalus such as brain tumors or subarachnoid hemorrhage, or any other diagnosed psychiatric or neurological problem that could have introduced confounding factors, were excluded from the study.

We studied 31 cases of iNPH. All of these patients showed probable iNPH with EI greater than 0.3, an insidious progression of symptoms (cognitive and gait dysfunction, urinary urgency), and CSF opening pressure less than 245 mmH_2O. Appropriately trained clinical psychologists or neurologists in our department evaluated the symptoms related to cognitive impairment. No patients showed any significant ischemic changes or demyelinating diseases.

We also studied 48 cases of AD. Recommendations from the National Institute on Aging Alzheimer's Association workgroups [6] were followed to diagnose probable AD. All patients showed an insidious onset of the disease, and significant concomitant cerebrovascular disease was ruled out. Among the patients who showed gait disturbances and/or urinary urgency, the CSF tap test was performed to rule out iNPH.

We also included 45 control cases in the study. The control participants were individuals aged more than 65 years with normal image findings from the same Arabic population. These patients were selected after they showed negative findings in screening tests for neurological or cognitive disorders after presenting with headaches.

Image acquisition

Brain CT scans (64 slices) of the participants were obtained using the routine brain CT protocol at our center. One researcher used Agfa HealthCare's Picture Archiving and Communications System (PACS) and the IMPAX suite software to calculate all the linear measures. These measures included the EI, defined as the quotient of the maximum distance between the frontal ventricular horns and the maximum interparietal length, and our new index (*VW_N*), which was based on the geometry of the inscribed circle of a triangle (Figure 1). After measuring the sides of the triangle, we obtained the inradius (r) distance and calculated *VW_N* as detailed in the next section.

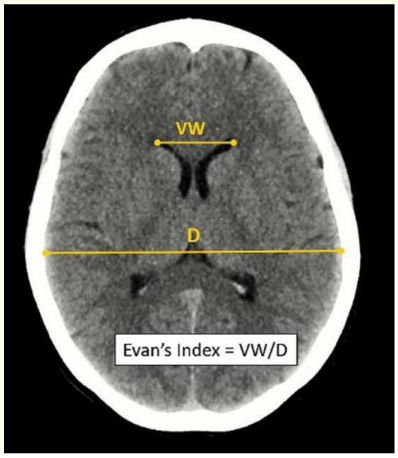

Figure 1A

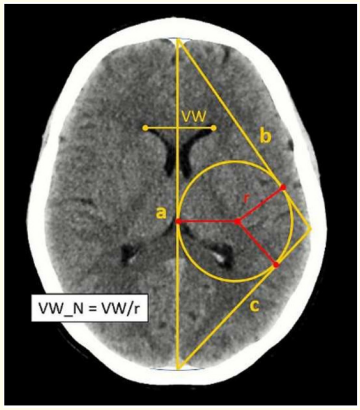

Figure 1B

Geometric model

We developed a model based on the geometry of the inscribed circle of a triangle. The inscribed circle was termed an incircle and was tangent to each of the triangle's sides. The center and radius of the incircle were termed the incenter and inradius, respectively. The incenter represented the point of concurrence of the triangle's angle bisectors.

The distances from the incircle to the three sides were all equal to the inradius. All triangles have inscribed circles, and every incircle is unique for every triangle. Thus, the formula for calculating the inradius is as follows:

$$r = \frac{\sqrt{s(s-a)(s-b)(s-c)}}{0.5(a+b+c)}$$

To calculate the radius, it is necessary to know the lengths of the three sides of the triangle, which represent the cranial shape, with "a" representing the anteroposterior distance and "b" and "c" representing the other two sides of the triangle with the vertex in the most lateral part of the parietal bone in the axial plane (Figure 1).

This new measure can be used to calculate a new linear proportion (VW_N) similar to EI that considers both the anteroposterior axis and the transverse axis of the skull: $VW\_N = VW/r$.

Statistical analysis

Descriptive statistics were calculated for the 124 individual neurological cases constituting the study population (Table 1). To determine whether EI and the newly developed index, VW_N, could distinguish between iNPH and AD, nominal logistic regression models were used to predict diagnosis. ROC curves were generated to determine how well the indices were able to differentiate between the iNPH and AD cases. The one-way analysis was conducted to explore the distribution of continuous indices across the two pathologies graphically and determine cutoff values. Analyses were performed using JMP Pro version 13 software, and statistical significance was determined at an $\alpha = 0.05$ level. This study was approved by the King Faisal Specialist Hospital and Research Center Institutional Review Board.

Results

The overall study population included 124 participants, including 31 (25%) patients with iNPH, 48 (38.7%) patients with AD, and 45 (36.3%) healthy controls (Table 1). The mean age was the lowest (72 ± 6 years) in the iNPH group and the highest (76 ± 7 years) in the AD group. While just over half (58.3%) of the AD patients were females, 25.8% of the iNPH patients and 71.1% of the healthy controls were females. The mean EI for the iNPH group was 0.39 ± 0.04, compared to 0.33 ± 0.05 for the AD group and 0.26 ± 0.04 for the control group. The mean VW_N index was 1.81 ± 0.20 for the iNPH group, 1.53 ± 0.2 for the AD group, and 1.24 ± 0.2 for the control group (Table 1).

	iNPH[e]	AD[f]	Control
No. of patients	31	48	45
Age (y) (± SD)	72 ± 6	76 ± 7	74 ± 7
Men	23	20	13
Women	8	28	32
EI[a] (±SD)	0.39 ± 0.04	0.33 ± 0.05	0.26 ± 0.04
VW_N[b] (±SD)	1.81 ± 0.2	1.53 ± 0.2	1.24 ± 0.2
VI[c] (±SD)	1.11 ± 0.12	0.98 ± 0.13	0.72 ± 0.10
r[d] (mm) (±SD)	27.8 ± 1.3	27.6 ± 1.1	27.3 ± 1.3

Table 1: Demographic characteristics and brain measurements.

[a]EI = Evans' index; [b]VW_N = Normalized measurement; [c]VI = Ventricular index ([frontal ventricular width + intercaudate width + III ventricle width + sella media width + temporal horn width)/ maximum parietal width]); [d]r = Inradius (mm); [e]iNPH = Idiopathic normal pressure hydrocephalus; [f]AD = Alzheimer disease.

Nominal logistic regression models were generated to observe the predicted probability of iNPH or AD diagnosis as a function of the EI and VW_N indices (Table 2). The value of the index in each model had a significant effect on the predicted probability of diagnosis. Figure 2A depicts the predicted probability of an AD diag-

nosis based on the EI value, while figure 2B depicts the predicted probability of an AD diagnosis based on the value of the VW_N index.

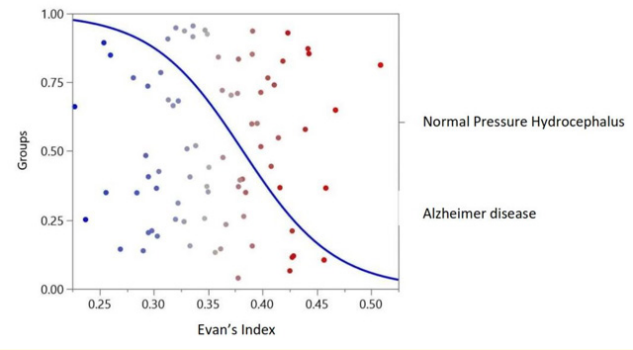

Figure 2A: Logistic fit of diagnosis by Evans' index.

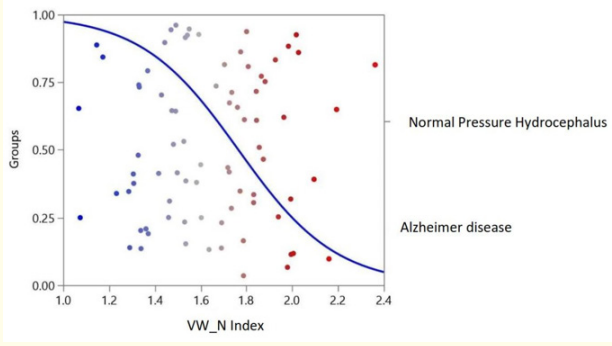

Figure 2B: Logistic fit of diagnosis by VW_N index.

For EI, the area under the receiver operating characteristic curve (AUC) value for the probability that a randomly selected individual from the AD group had an index value indicating more considerable suspicion than that for a randomly chosen individual from the iNPH group was 0.803 (Table 2). Figure 3 depicts the corresponding measurement with the VW_N index, and the AUC value was 0.802, indicating similar probabilities with the two indices.

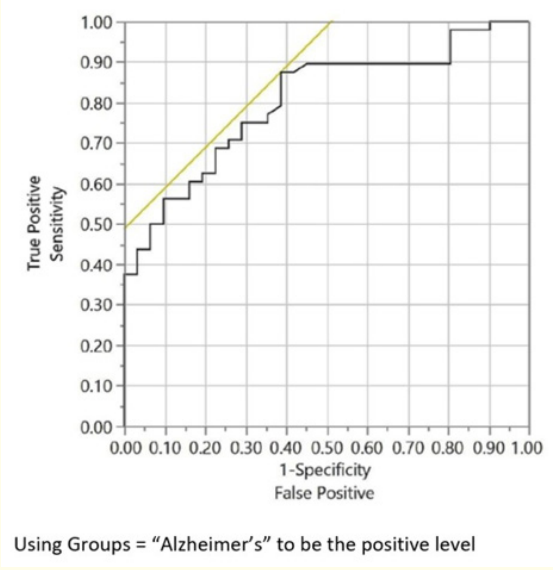

Figure 3A: Receiver operating characteristic curve for Evans' index.

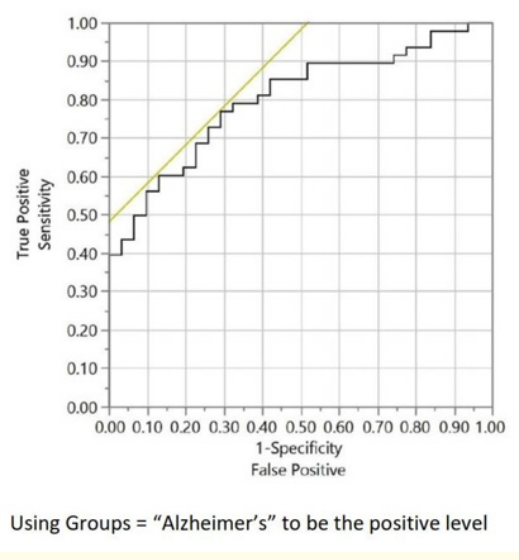

Figure 3B: Receiver operating characteristic curve for the VW_N index.

Parameter	AIC* Value	Chi-square	R^2 Value	df	p-value	AUC
Evans Index model	86.7	23.3	0.22	1	< 0.0001	0.803
VW_N Index model	88.4	21.6	0.20	1	< 0.0001	0.802

Table 2. Evans and VW_N indices as predictors of iNPH and AD diagnoses.

*AIC = Akaike Information Criterion.

Box plots of the predictor index variables by group (AD and iNPH) were used to estimate cutoff values for the indices to differentiate between the two diagnoses (Figure 4). The median value of the EI index for the AD group was 0.33 compared to 0.40 in the iNPH patients. For VW_N, the AD patients had a median value of 1.50 compared to 1.81 for the iNPH group. Cutoff values for distinguishing between AD and iNPH in the study population were determined to be 0.36 for EI and 1.6 for VW_N.

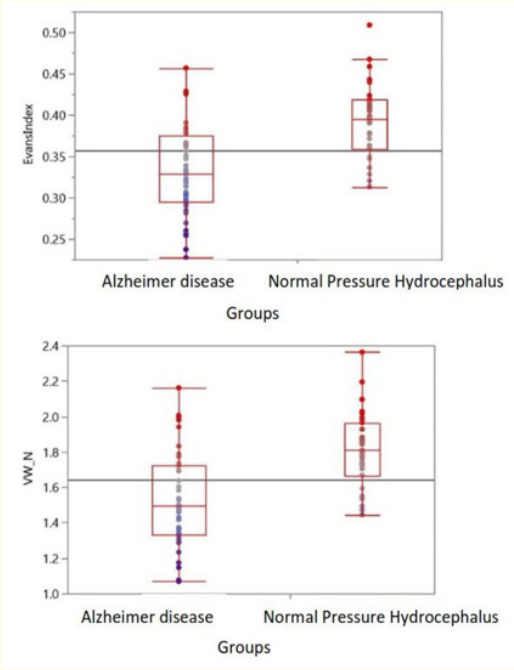

Figure 4: Graphic depiction of Evans' index and VW_N index by AD vs. iNPH groups.

Discussion

Radiological studies have a primary diagnostic value for evaluating patients with progressive dementia, unsteady gait, and urinary incontinence for distinguishing iNPH and AD. One of the main diagnostic features is the ventricular dilatation as one of the classic features common to AD and iNPH. Although the physiopathology of ventricular dilatation in the two diseases is very different, neuroradiology remains one of the fundamental techniques for the diagnosis of this condition. Ventricular dilatation shows very different patterns in the two conditions, with global dilatation predominating in NPH and increased parahippocampal fissures appearing in AD [1]. Because of this difference in the ventricular dilatation pattern, our main hypothesis was that ventricular size in the frontal horn was different between EA and iNPH. To demonstrate this hypothesis, we used a tool that measures the ventricular dilatation through the frontal horn, EI. Because EI only takes into account the interparietal distance for the calculation, we thought that a model that also took into account the anteroposterior distance of the skull would provide an improved calculation of the ventricular ratio.

For this purpose, we created a geometric model based on the inscribed circle of a triangle. The resulting measurement, the inradius, in addition to the interparietal distance of the EI, takes into account the anteroposterior distance of the skull and the proportional relationship between both of them (Figure 1). Similar to the EI, this new measurement was used to divide the frontal horn distance. This significantly improved the information contained in the index by providing a proportional measurement of the skull, which has not yet been described, and can be used in any calculation where the cranial shape needs to be considered. This model is not perfect, because although the anteroposterior distance is measured in the plane where there is maximum frontal horn dilation and in the protocol for cranial CT scans, the cuts are parallel to the cranial base and there is always a small variation in the sagittal plane from which the axial cuts are taken. Nevertheless, the inradius is a linear measure that is proportional to the cranial shape. Thus, these are two similar indices, with ours showing a better relationship with the cranial shape, that were used to better distinguish AD and iNPH. As shown in the results, both indices could differentiate between AD and iNPH cases from our series. Moreover, the area under the ROC curve values for both indices was similar (0.803 vs. 0.802).

At this point, it is important to note that the cases studied with EI and our geometric model (VW_N) were previously selected and differentiated with a precise clinical diagnosis, and none of them presented with both pathologies at the same time, which can occur in normal clinical practice. Therefore, the final sensitivity and specificity of the results of both indices in the general population are unknown. The differences in the size of the dilated frontal ventricular horn in AD and iNPH can confirm the hypothesis of the study. Thus, in cases of iNPH, the ventricular enlargement is greater than that in AD. The cutoff EI to differentiate between the two was 0.36 and the cutoff VW_N was 1.6. Both methods were found to be equally useful in differentiating patients from normal participants (EI < 0.3 and VW_N < 1.3) (Figure 4).

Although EI is not the most accurate method for measuring brain ventricles in iNPH [7], in comparison with techniques such as ventricular volume measurement [8-15], it remains a good initial radiological tool to assess ventricular enlargement and is well supported by international guidelines [5]. Moreover, the objective of our study was not to study iNPH exhaustively but to differentiate it from AD, which shows a very different pattern of ventricular dilatation, measures based on the frontal ventricular horns are of particular interest.

One of the advantages of using EI or VW_N is its easy applicability and reproducibility. Although there are other biomarkers like callosal angle [16] or disproportionate sulci [2], these are difficult to interpret or measure, especially when comparing cases or studies.

Another interesting aspect that we can affirm is that the creation of an index (VW_N) that is theoretically better than EI does not improve the capacity to differentiate between AD and iNPH. In this sense, cranial morphology may not be related to the severity of ventricular enlargement, although it would be premature to make this statement only based on this research. Clarifying how the anteroposterior measure should be improved is one of the topics we plan to study in the future.

Conclusion

The size of the dilated frontal ventricular horn is different in AD and iNPH, and brain linear measurements can differentiate between them. We developed a novel geometric model that obtains a linear measurement proportional to the skull shape that demonstrated this difference. We show that our novel geometrical method is similar to EI for identifying AD and iNPH. Further research and validation for other ventriculomegaly pathologies are required to increase the usage of the geometrical method. Using this model or EI, an initial radiological diagnosis can be made to differentiate between AD and iNPH.

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