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Imaging findings of IIH: The value of MRI in predicting the presence of disease

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Abstract

Research Question
Can MR imaging findings predict the presence of IIH, and can we reproduce and reinforce existing knowledge in literature.

Background, Significance, and Rationale
Idiopathic intracranial hypertension (IIH) is a condition characterized by an increase in cerebrospinal fluid (CSF) with a lack of identifiable etiology. We believe that MR imaging findings can predict the presence of IIH and we attempted to reproduce and reinforce existing knowledge in the literature.

Methods and Methods
This study was a retrospective data analysis of MRI reports completed during 2020 at John Peter Smith hospital (Fort Worth, TX). Reports containing "Idiopathic intracranial hypertension" were reviewed and patients with a lumbar puncture confirming the diagnosis were included. All cases were de-identified and randomized. These MRI studies were reviewed by three neuroradiologists who were blinded to the diagnoses. The presence or absence of each of four characteristic imaging findings were noted. Inter-rater reliability (IRR) and Odds Ratios (OR) were analyzed for each finding using a generalized linear mixed model.

Results
Our results demonstrated substantial agreement amongst radiologists when identifying empty pituitary sella, enlarged optic nerve sheaths, and posterior globe flattening (IRR value >0.6). However, there was only moderate agreement amongst radiologists when assessing bilateral transverse sinus stenosis (κ value 0.569). ORs for each imaging finding were statistically significant (OR range 10.8-49.3). Posterior globe flattening had the highest OR (49.3) and was not observed in controls.

Conclusions
Our results reinforced existing evidence that there are characteristic imaging findings on MRI that suggest a diagnosis of IIH. A limitation to this study was the lack of vascular imaging such as MR Venography, which is likely responsible for the low IRR in identifying bilateral transverse sinus stenosis. A future retrospective study could include vascular imaging.

Research Question

Primary Aim: To assess the predictive value of MRI imaging findings in diagnosing IIH by analyzing characteristic features such as empty pituitary sella, bilateral transverse sinus stenosis, enlarged optic nerve sheaths, and posterior globe flattening.

Secondary Aims:

1. To evaluate inter-rater reliability among neuroradiologists in identifying MRI findings associated with IIH.
2. To determine the odds ratios of specific MRI findings for diagnosing IIH compared to normal controls.
3. To discuss the implications of MRI imaging in the early detection and management of IIH, considering its impact on patient outcomes and healthcare costs.
4. To identify potential areas for future research aimed at refining diagnostic approaches for IIH, including the incorporation of vascular imaging techniques.

Introduction

Idiopathic intracranial hypertension (IIH) is a condition marked by an increase in cerebrospinal fluid (CSF) without a distinctly identifiable structural cause or etiology. [1] [2] [3]IIH predominantly affects young, obese female patients and manifests through primary symptoms such as visual disturbances and progressively worsening and more frequent headaches. Additional symptoms include dizziness, back pain, neck pain, pulsatile tinnitus, pulse-synchronous tinnitus, and papilloedema. [2] [4] [5] [6] IIH has been denoted by diverse names, encompassing serous meningitis, pseudotumor cerebri, intracranial pressure without a brain tumor, and benign intracranial hypertension [7]. The term "benign" has been omitted over the past few decades due to the potential for blindness in up to 10% of cases [8]. In the Western hemisphere, the annual incidence of IIH is 0.9/100,000 in the general population and 3.5/100,000 in females aged 15-44 [6]. As the prevalence of obesity rises, the incidence of this condition is expected to increase [2]. The estimated annual cost of IIH in the United States, considering recurrent hospitalizations and its impact on relatively young patients' workforce productivity, exceeds 444 million dollars [9].

The journey to diagnose IIH is intricate, often marked by delays and primarily reliant on exclusion. Comprehensive guidelines for diagnosis, treatment, and management were not accessible until as recently as 2018 [5]. IIH is identified when a patient exhibiting characteristic symptoms presents with a CSF opening pressure exceeding 25 cm H2O on lumbar puncture (LP), accompanied by normal CSF contents and the absence of any known secondary cause (e.g., medication, infection, or neoplasm).

The disease's pathophysiology remains idiopathic, with resistance to CSF outflow seemingly playing a significant role[10]. Various factors, including increased cerebral venous pressure, endocrine dysfunction, vitamin A deficiency, and excess CSF production, have been explored as potential causes; however, a definitive etiology remains elusive [6].

Treatment for IIH varies based on the patient's visual acuity. In cases where blindness is a significant threat, immediate treatment options include CSF diversion or optic nerve sheath

fenestration [11,12]. If visual testing is normal, initial management typically involves weight loss and medical therapy with acetazolamide[12]. A weight loss of 15% can induce disease remission with complete symptom resolution, and acetazolamide has shown significant improvement in patient symptoms[3,13]. Bariatric surgery is also considered an effective treatment option when diet and exercise alone prove insufficient for weight loss[14]. The efficacy of these treatments in reducing morbidity underscores the importance of early diagnosis, which can be facilitated through neuroimaging.

Various neuroimaging features suggest increased intracranial pressure (ICP), prompting an evaluation for IIH. Recent research indicates that distinctive findings, including an expanded and vacant pituitary sella, flattening of the posterior globe, severe bilateral transverse sinus stenosis, and enlarged optic nerve sheaths, are noteworthy and exhibit high specificity[5,7,15].

The significance of this work lies in its potential to significantly impact the diagnosis and management of Idiopathic Intracranial Hypertension (IIH), a condition associated with increased cerebrospinal fluid pressure without an identifiable cause. Through the analysis of MRI imaging findings, this research aims to provide clinicians with a more precise and reliable method for identifying IIH. Currently, IIH diagnosis primarily relies on clinical symptoms, ophthalmological assessments, and lumbar puncture measurements of cerebrospinal fluid pressure. However, diagnosing IIH through radiology remains challenging due to the absence of specific imaging biomarkers and the reliance on indirect signs of increased intracranial pressure. This difficulty in diagnosing IIH by radiology highlights the need for improved imaging techniques and diagnostic criteria. By identifying specific MRI findings predictive of IIH, this study seeks to address this diagnostic gap and provide clinicians with valuable tools for early detection and intervention. Furthermore, the availability of MRI images, coupled with the recognition of challenges in IIH diagnosis, underscores the importance of investigating factors that may contribute to accurate diagnosis. By elucidating the relationship between MRI findings and IIH, this research aims to enhance our understanding of the disease process, improve diagnostic accuracy, and ultimately optimize patient care. Through this comprehensive approach, we aim to bridge the gap

between clinical presentation and radiological diagnosis, thereby facilitating earlier intervention and better outcomes for individuals with IIH.

Methods and Methods

Population

This study was a retrospective analysis of MRI reports completed during 2020 at John Peter Smith hospital (Fort Worth, TX). Any MRI report containing the phrase “Idiopathic intracranial hypertension” was reviewed and patients with a lumbar puncture confirming the diagnosis of IIH were included. The study sample was 64 IIH cases and 41 normal MRI brains as a control. Controls were identified by those with symptoms that warranted MR imaging, but had no abnormal findings. All cases were de-identified and randomized for HIPPA compliance, as well as to stay in line with our IRB approval. These MRI studies were reviewed by three different board-certified neuroradiologists who were blinded to the diagnoses. The presence or absence of four imaging findings was noted—empty pituitary sella, posterior globe flattering, bilateral transverse sinus stenosis, and enlarged optic nerve sheaths. Figure 1 demonstrates an empty pituitary sella and Figure 2 demonstrates enlarged optic nerve sheaths. Figure 3 demonstrates posterior globe flattening and Figure 4 demonstrates bilateral transverse sinus stenosis.

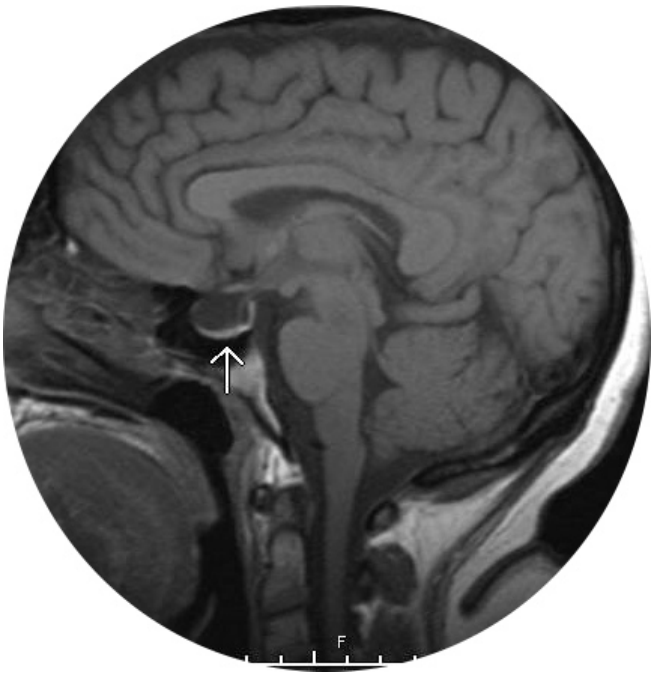

Figure 1: An expanded, empty pituitary sella (arrow) in a patient with IIH.

Figure 2: Expanded CSF spaces within the enlarged bilateral optic nerve sheaths (arrows) in a patient with IIH.

Figure 3: Posterior globe flattening and papilledema (arrows) in a patient with IIH.

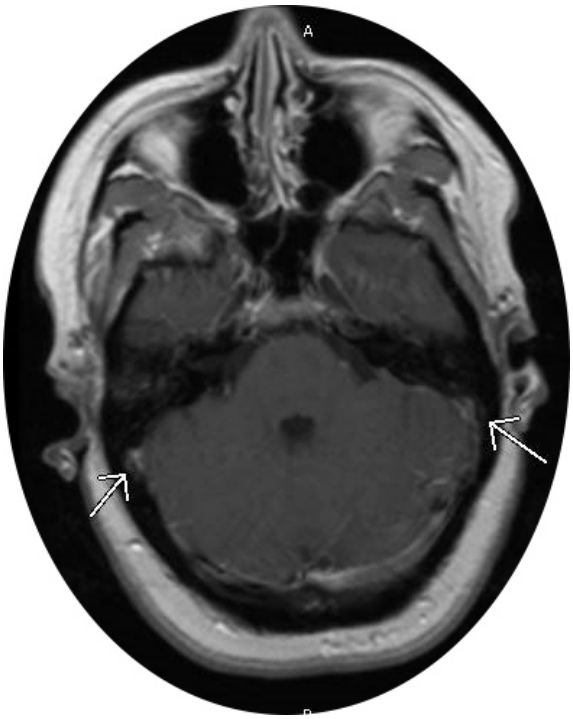

Figure 4: Bilateral transverse dural venous sinus stenosis (arrows) in a patient with IIH.

Statistical Methods

Inter-rater reliability (IRR) was assessed across the three radiologists to determine reliability of imaging findings between the radiologists; IRR was assessed across the entire population--both patients with IIH and patients with normal imaging.

To account for the repeated assessments by each radiologist, generalized linear mixed models were performed. Models assessing the probability of having empty pituitary sella, bilateral sinus stenosis, enlarged optic nerve sheaths, or posterior globe flattening and being diagnosed with IIH were performed.

Results

Table 1 provides an overview of IRR values by diagnosis and population (i.e. overall, IIH, and normal). When assessing solely normal patients, there was no significant agreement among radiologists (IRR values <0.6). Similarly, there was no significant agreement among radiologists when diagnosing bilateral transverse sinus stenosis (IRR values <0.6). There was however substantial agreement among radiologists when diagnosing empty pituitary sella, enlarged optic nerve sheaths, and posterior globe flattening (IRR values >0.6) in both the overall and IIH populations.

Table 1. Inter-Rater Reliability of Radiologist Diagnosis

	All Subjects N = 105	**IIH Subjects N = 64**	**Normal Subjects N = 41**
Empty Sella	0.959	>0.999	0.599
Bilateral Transverse Sinus Stenosis	0.569	0.521	0.238
Enlarged Optic Nerve Sheaths	0.827	0.914	-0.0789
Posterior Globe Flattening	0.705	0.621	-0.025

Results of the generalized linear mixed models are detailed in **Table 2**. The ORs of being diagnosed with empty pituitary sella, bilateral transverse sinus stenosis, enlarged optic nerve sheaths, and posterior globe flattening were significantly higher in patients with IIH ($p < 0.001$). The odds of being diagnosed with empty pituitary sella was 19.699 times higher in patients with IIH when compared to normal patients (95% CI: 9.055, 42.854). The odds of being diagnosed with bilateral transverse sinus stenosis was 10.839 times higher in patients with IIH when compared to normal patients (95% CI: 5.324, 22.064). The odds of being diagnosed with enlarged optic nerve sheaths was 18.513 times higher in patients with IIH when compared to normal patients (95% CI: 8.811, 38.896). The odds of being diagnosed with posterior globe flattening was 49.302 times higher in patients with IIH when compared to normal patients (95% CI: 15.017, 161.865).

Table 2. Results of Generalized Linear Mixed Model Assessing Imaging Findings by Idiopathic Intracranial Hypertension Status				
		Odds Ratio	**95% Confidence Interval**	**P-Value**
a.) Probability of Being Diagnosed With An Empty Pituitary Sella				
Patient Status				
	Idiopathic Intracranial Hypertension	19.699	(9.055, 42.854)	<.0001
	Normal	*Reference*	*Reference*	*Reference*
b.) Probability of Being Diagnosed With Bilateral Transverse Sinus Stenosis				
Patient Status				
	Idiopathic Intracranial Hypertension	10.839	(5.324, 22.064)	<.0001
	Normal	*Reference*	*Reference*	*Reference*
c.) Probability of Being Diagnosed With Enlarged Optic Nerve Sheaths				
Patient Status				
	Idiopathic Intracranial Hypertension	18.513	(8.811, 38.896)	<.0001
	Normal	*Reference*	*Reference*	*Reference*
d.) Probability of Being Diagnosed With Posterior Globe Flattening				
Patient Status				
	Idiopathic Intracranial Hypertension	49.302	(15.017, 161.865)	<.0001
	Normal	*Reference*	*Reference*	*Reference*

Discussion

In this study we reinforced existing evidence that the presence of an empty pituitary sella, bilateral transverse sinus stenosis, enlarged optic nerve sheathes, or posterior globe flattening are predictive of the presence of IIH. The results showed substantial agreement among the neuroradiologists when identifying an empty pituitary sella, enlarged optic nerve sheathes, and posterior globe flattening. Posterior globe flattening had the highest odds ratio and was not observed in any of the controls. Notably, there was only modest agreement when assessing for the presence of bilateral transverse sinus stenosis. Notable limitations for this study include the lack of vascular imaging such as CT or MR venography which could account for the lack of agreement when assessing for bilateral transverse sinus stenosis. This lack of agreement suggests against the routine use of this finding in excluding the presence of IIH in the absence of venography. A future study could assess venography alone or combined with these findings to predict the presence of IIH.

The observed MRI findings suggestive of IIH likely stem from a complex interplay of pathophysiological mechanisms underlying the condition. For instance, the presence of an empty pituitary sella may reflect the downward displacement of the pituitary gland due to increased intracranial pressure, leading to compression and subsequent enlargement of the optic nerve sheaths. This phenomenon could result from altered CSF dynamics and venous congestion within the intracranial compartment, contributing to the observed MRI abnormalities.

The variability in the agreement among neuroradiologists in identifying these MRI features could be attributed to several factors. Differences in radiologists' experience, training, and interpretation criteria may influence their ability to detect subtle imaging changes associated with IIH. Additionally, variations in MRI protocols, image quality, and patient characteristics could introduce inherent challenges in accurately assessing these features across different radiology groups. The predictive value of these MRI findings for diagnosing IIH raises intriguing questions about their underlying biological significance. It is conceivable that these imaging

biomarkers reflect distinct pathological processes within the intracranial compartment, such as optic nerve inflammation, venous sinus thrombosis, or structural alterations in the optic nerve sheaths. However, further research is needed to elucidate the mechanistic underpinnings of these MRI findings and their relationship to IIH pathophysiology.

Regarding the clinical utility of these MRI findings, while they hold promise as diagnostic indicators for IIH, their practical application in real-world clinical settings warrants careful consideration. Clinicians must weigh the sensitivity, specificity, and reproducibility of these imaging biomarkers against other diagnostic modalities and clinical parameters when making diagnostic and therapeutic decisions for patients with suspected IIH. Confirmation of these MRI findings in the context of IIH diagnosis aligns with and reinforces existing literature on the subject. However, it also underscores the need for continued exploration and validation of novel imaging biomarkers and diagnostic algorithms to enhance the accuracy and reliability of IIH diagnosis and management.

In essence, the observed MRI findings in this study accurately reflect what was known about IIH, while variations in radiologists' interpretation and clinical contexts may influence their diagnostic utility later on. Further investigation into the biological mechanisms underlying these imaging biomarkers and their clinical implications is warranted to advance our understanding and management of IIH.

Future Directions

- Investigate the mechanistic underpinnings of MRI findings associated with IIH to elucidate their biological significance and potential as diagnostic biomarkers.
- Explore inter-observer variability among radiologists from different institutions to assess the generalizability of MRI-based diagnostic criteria for IIH.
- Conduct prospective studies to validate the predictive value of MRI findings in diagnosing IIH and assess their sensitivity and specificity compared to other diagnostic modalities.

- Investigate the role of advanced imaging techniques, such as MR venography, in conjunction with MRI findings to enhance diagnostic accuracy and refine IIH diagnostic algorithms.
- Conduct multi-center collaborative studies to validate and refine MRI-based diagnostic criteria for IIH across diverse patient populations and healthcare settings.
- Explore the feasibility of incorporating MRI findings into clinical practice guidelines and algorithms for the diagnosis and management of IIH, with the aim of standardizing diagnostic approaches and improving patient care.

Conclusion

Overall, this study reinforced existing evidence that these MR findings are suggestive of IIH and further workup should be pursued in the setting of a characteristic clinical presentation.

Empty pituitary sella, bilateral transverse sinus stenosis, enlarged optic nerve sheathes, and posterior globe flattening are predictive of the presence of IIH. These findings have substantial inter-observer reliability, except for bilateral transverse sinus stenosis, which only had modest agreement.

Compliance

We confirm that this study was conducted in full compliance with the regulations and guidelines set forth by the North Texas Institutional Review Board (IRB) and adhered to the research standards of the JPS Health Network. All necessary ethical considerations, including informed consent procedures, participant confidentiality, and regulatory reporting requirements, were strictly followed throughout the course of this research.

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