ORIGINAL ARTICLE

Neuroimaging Features of Idiopathic Intracranial Hypertension Persist After Resolution of Papilloedema

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ABSTRACT

Papilloedema is a key clinical finding in the diagnosis of idiopathic intracranial hypertension (IIH). However, newly proposed criteria allow diagnosis without papilloedema only if certain neuroimaging features are present. It is currently unclear if these findings persist upon resolution of papilloedema and IIH. A retrospective chart review identified three groups of patients (six per group) who had received orbital imaging within 4 weeks of fundoscopic examination: (1) IIH patients without active papilloedema, (2) IIH patients with active papilloedema, and (3) patients with no history of IIH or papilloedema. All magnetic resonance imaging (MRI) scans were graded by a neuroradiologist who was blinded to clinical status. Neuroimaging features were compared by using the Kruskal-Wallis one-way analysis of variance. Measurements of sellar and optic nerve configuration showed a statistical trend with papilloedema status. For the control group versus the active papilloedema group, the values were 0.0597 and 0.0621, respectively. For the control group versus the resolved papilloedema group, the values were 0.0485 and 0.0512, respectively. However, globe and sellar *p* values for the resolved papilloedema group versus the active papilloedema group were 1.000 and 0.6023, respectively, and not significant. Sellar and globe configuration suggest that a statistical trend for persistence after papilloedema has resolved and intracranial pressure (ICP) has normalised. Careful clinical correlation and fundus examination are essential because some of these neuroimaging features can be seen in normal patients and those with resolved IIH, and their presence on MRI may not necessarily indicate active disease or elevated ICP.

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Introduction

Idiopathic intracranial hypertension (IIH) is characterised by elevated intracranial pressure (ICP) without an identifiable aetiology. Papilloedema is a key clinical finding associated with IIH. Higher grades of papilloedema correlate with more severe vision loss,¹ and the presence, progression, and subsequent resolution of papilloedema is used to both diagnose and monitor the disease.² The presence of papilloedema is generally considered a surrogate marker of elevated ICP >20 cm H₂O¹ and is readily observed on careful ophthalmoscopic examination. Over the past decade, a body of literature has emerged describing characteristic neuroimaging features of both IIH and papilloedema,^{3–8} including empty sella, posterior globe flattening, distention of the perioptic subarachnoid space (SAS), transverse sinus stenosis, and diffusion-weighted imaging (DWI) hyperintensity of

the optic nerve head (ONH). The sensitivity and specificity of these findings vary greatly, depending upon prior probability, the quality of the magnetic resonance imaging (MRI), and the reader.^{3–8}

The diagnosis of IIH previously required fulfilling the modified Dandy criteria,⁹ which had not mandated the presence of papilloedema. These criteria were recently revised in light of recent work and now include the presence of neuroimaging features to secure the diagnosis, particularly when papilloedema is not present (IIH without papilloedema). The specific anatomic and physiologic mechanisms underlying these structural changes are not entirely clear and remain speculative.

Although these neuroimaging features are well described in patients with active papilloedema and IIH,^{3,5,10} it is unclear if they persist once papilloedema has clinically resolved. This information has

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implications for the diagnosis of patients who present with symptoms suggestive of intracranial hypertension but without active papilloedema. The resolution or persistence of neuroimaging features with resolution of papilloedema and normalisation of elevated ICP might lend insight into the underlying mechanisms behind these changes. This issue has been poorly studied, in part because repeat neuroimaging is only rarely performed in IIH once the papilloedema has resolved, and there is no evidence of ongoing intracranial hypertension.

We performed a retrospective cross-sectional proof-of-concept study to determine whether neuroimaging features of IIH persist following resolution of papilloedema.

Materials and methods

Data collection

Approval for the study was obtained from our institutional Human Research Protection Office prior to data accumulation, and all Health Insurance Portability and Accountability Act (HIPAA) regulations regarding the use of personal health information were strictly followed.

A comprehensive retrospective chart review of our university-based neuro-ophthalmology clinic database was performed. We identified three groups of patients seen between 2009 and 2013: (1) study group with no active papilloedema by modified Frisen scale grading¹¹ who had previous fundoscopic and clinical evidence of IIH; (2) study group with active papilloedema who met Dandy criteria for IIH, or who had strong clinical support for the diagnosis of IIH but did not receive lumbar puncture (LP); and (3) control group with no history of papilloedema or increased ICP. Three groups of 6 were age-matched for a total of 18 female patients. All were age-matched to within 4 years, with range 15–55. Subjects were not matched for body mass index (BMI) because there is little evidence that the variable independently factors into the graded MRI parameters. Patients with resolved or active papilloedema all had a typical body habitus for IIH, with BMI >25.¹² We included only those who had received magnetic resonance imaging (MRI) with dedicated orbital images within 4 weeks of fundoscopic evaluation for papilloedema. Subjects in the control group were thoroughly evaluated for other

suspected neurological conditions. Normal ICPs were presumed for the first study group by a lack of signs and symptoms of ICP (excluding non-specific headache) and no papilloedema. Since this was intended as a proof-of-concept study, we sought to be more rather than less inclusive. This meant that Group 1 included a few subjects who had not originally been formally evaluated for IIH, but who had evidence of previous papilloedema by fundus examination and who would be considered typical for IIH in terms of presentation and demographics. The presumption was that these were patients who had previously had IIH but had spontaneously resolved, which is part of the natural history of this condition.¹ Their fundus examinations showed clear-cut evidence of bilateral optic disc swelling, in a pattern typically observed after papilloedema resolves.

The following demographic and clinical data were collected from all patients (if applicable): gender, ethnicity, age, diagnosis, time to resolution of papilloedema, and date of LP (Table 1).

A neuroradiologist blinded to clinical status and study group assignment graded the following MRI parameters: optic nerve sheath (ONS) thickness, optic nerve thickness (ONT), subarachnoid space (SAS) around the optic nerve, ONT/SAS ratio, sellar configuration, and ONH appearance (globe configuration and ONH enhancement). These parameters were graded based on a pre-determined scale (Table 2), which has been used previously to perform both quantitative and qualitative analyses of the imaging.¹³ MR images were evaluated as follows: optic nerve and globe configuration on axial T2-weighted MR (slice thickness 3–5 mm); sellar configuration on sagittal T1-weighted MR (slice thickness 5 mm); ventricular size and prominence of cortical sulci on axial T1-weighted and T2-weighted MR (slices through brain).

Table 1. Patient data for each of the three study groups.

Characteristic	Controls	Resolved papilloedema	Active papilloedema
Number of patients	6	6	6
Age			
Mean	42	42	42
SD	13	14	12
CC:AA (ethnicity)	1:1	5:1	1:0
% Lumbar puncture	0%	67%	100%
Mean TRP (years)	—	4.4	—

Note. CC:AA = Caucasian:African American; SD = standard deviation; TRP = time to resolution of papilloedema.

Table 2. MRI features analysed and grading scheme used.

MRI grading	
MRI feature	Grading
Sellar configuration	1 = normal (unflattened pituitary); 2 = <50% flattened; 3 = >50% flattened; 4 = completely flattened pituitary
ONT	Measured in mm
ONS thickness	Measured in mm
SAS	Measured in mm, ONS thickness – ONH thickness
Globe configuration	1 = normal outwards convexity of sclera at attachment to optic nerve; 2 = flattening of sclera; 3 = protrusion of ONH into globe (concave towards globe)
ONH enhancement	0 = none; 1 = subtle; 2 = obvious but < muscle; 3 = equal to or > muscle

Note. ONT = optic nerve thickness; ONS = optic nerve sheath; SAS = subarachnoid space; ONH = optic nerve head.

Statistical analysis

Using each MRI parameter, the three groups were compared by non-parametric rank testing using the Kruskal-Wallis one-way analysis of variance.

Results

In the resolved papilloedema group, four of the six patients met the modified Dandy criteria for the diagnosis of IIH, including LP with elevated opening pressure at time of diagnosis. All had fundoscopic evidence of previous papilloedema, and the patients without prior LP had previous symptoms suggestive of IIH and fit the typical demographic profile. The time from resolution to the MRI ranged from 8 months to 10 years (mean: 4.4 years). If present, transient visual obscurations (TVOs) and pulsatile tinnitus had resolved in all patients by the time papilloedema had resolved. Three out of six patients from the resolved papilloedema group were still on treatment with Diamox when imaging occurred. Average papilloedema grade at the time of MRI before resolution was 3.1. Table 1 summarises the study group data.

The mean values of the collected MRI parameters for each of the three study groups were determined. *p* values comparing the groups were also calculated by Kruskal-Wallis test (Table 3). Scatterplots of raw data and bar graphs of group means comparing the

three study groups for globe configuration, sellar configuration, and cerebrospinal fluid (CSF) space were constructed (Figure 1). Two parameters, sellar configuration and optic nerve configuration, remained altered after resolution of papilloedema. For these parameters, the resolved group was no different from the active group, but demonstrated statistical significance (globe configuration) or a statistical trend (sellar configuration) from the control group. The active group also showed a statistical trend in both globe and sellar configuration as compared with the control group (Table 4). Figure 2 illustrates one patient in the resolved papilloedema group. The images demonstrate the persistence of sellar and globe configuration and decrease in optic disc papilloedema grade that occurred after resolution of papilloedema.

Discussion

The neuroimaging features associated with IIH have been recognised for some time, and are being refined with the advent of modern neuroimaging techniques. However, previous studies have primarily evaluated MRI findings in patients with active papilloedema and IIH, with ongoing elevated ICP.^{3,5,10} Our study is the first to assess the persistence of these findings in a group of patients with resolved papilloedema and presumably normal ICP.

Table 3. Mean values of the various MRI features for each of the three study groups.

MRI feature	Controls	Resolved papilloedema	Active papilloedema	<i>p</i> value by Kruskal-Wallis test
Sellar configuration	2.2	3.2	3.3	0.0824
ONS thickness	7.0	8.3	6.7	0.2148
CSF space	4.0	5.1	3.9	0.4358
Globe configuration	1.1	2.0	2.0	0.0956
ONH enhancement	0.4	0.6	1.0	0.2236

Note. ONS = optic nerve sheath; CSF = cerebrospinal fluid; ONH = optic nerve head.

p values comparing the groups were calculated by Kruskal-Wallis test (non-parametric rank testing).

Figure 1. Sellar configuration, globe configuration, and CSF space. Bar graphs of group means compare the three study groups for sellar configuration (A), globe configuration (B), and CSF space (C).

Table 4. *p* values calculated by Kruskal-Wallis test (non-parametric rank testing) comparing study groups for globe configuration and sellar configuration.

Compared groups	<i>p</i> values	
	Globe configuration	Sellar configuration
Resolved vs. active	1.000	0.6023
Control vs. active	0.0597	0.0621
Control vs. resolved	0.0485	0.0512

None of the MRI parameters among the three groups were found to be significantly different. However, the low *p* values of sellar configuration and optic nerve configuration (including globe flattening and ONH protrusion) suggest a possible trend. Further exploratory analysis revealed that these two findings persist after visible papilloedema has resolved (Table 4). These results are in line with previously revised diagnostic criteria for IIH⁴ and further support that neuroimaging, specifically the persistence of an empty sella and posterior globe flattening, may be useful for IIH diagnosis even after the resolution of papilloedema and the normalisation of ICP. The difference between groups was strongest for the sellar

configuration. Previous studies have found persistent distention of the SAS in IIH without papilloedema,⁴ but we found no persistent dilation of perioptic SAS in the resolved papilloedema group. This apparent discrepancy can be explained by Table 3, in which the individual group means for CSF space reveal that SAS was in fact larger in the resolved group compared with the active group. However, these differences might simply be attributable to the underlying differences in ONS thickness among the patients. It is possible that our study's image quality and number of patients may have limited the persistence of these two parameters between resolved and active papilloedema groups. Mean globe configuration was also determined to be the same between resolved and active groups (Table 2), but peripapillary gliosis and the resulting disc elevation can account for the similarity.²

The strengths of the study include the consistency of findings across all three groups; the evaluation by an experienced neuroradiologist masked to the clinical status of the subjects; and the inclusion of a

Figure 2. Magnetic resonance imaging, active versus resolved papilloedema. One patient from the resolved papilloedema group underwent MRI during active papilloedema and after resolution of papilloedema (images taken 2 years apart). MRI demonstrated empty sella both before (A) and after (B) resolution of papilloedema. MRI also demonstrated protrusion of the ONH into the globe both before (C) and after (D) resolution of papilloedema. Images of the patient's left optic disc also demonstrated grade III papilloedema (E) and grade 0 papilloedema (F) taken within 4 weeks of the above MRI images.

control group with no active or previous papilloedema. Our study had the following limitations. First, we presumed normalisation of ICP in the resolved papilloedema group and did not perform LP for formal measurement. However, the absence of papilloedema and the lack of more specific signs and symptoms of elevated ICP (i.e., TVOs, pulsatile tinnitus, sixth nerve palsy) would argue for normal intracranial pressure. Although all of the patients in the resolved papilloedema group did report headache, previous studies have shown that most patients with IIH have co-existing migraines that persist even when the disease resolves (i.e., no papilloedema and normal ICP confirmed by repeat LP).¹⁴ We could not ethically justify performing lumbar puncture in all subjects to confirm normal ICP. Further, the range of what is considered “normal” opening pressure has widened considerably in recent years,^{4,15} so an isolated opening pressure in the absence of papilloedema and no symptoms of elevated ICP is of relatively limited diagnostic value.

Second, two patients in the resolved papilloedema group failed to fulfill the modified Dandy criteria due to lack of LP but were included because they had initially presented with the classic clinical features and demographic profile of IIH (gender, body habitus, and papilloedema). At time of

presentation to the neuro-ophthalmology clinic, their original symptoms had resolved, and LP was deferred. It is possible that these patients had an occult, chronic meningitis, a condition that cannot be completely excluded without an LP. However, MRI showed no leptomeningeal enhancement. These patients had increased BMI and followed a benign course without any systemic symptoms or meningeal signs. It is also possible that these patients had drusen or pseudopapilloedema. However, all patient fundus photos were carefully reviewed for clinical and study purposes and revealed clear evidence of previous disc swelling without evidence of drusen or pseudo-papilloedema. Even if they did not have true IIH, we have still demonstrated that the neuroimaging features of optic disc swelling persist after the oedema resolves.

We also acknowledge that our sample size was small. Further research with a larger sample size could demonstrate statistically significant differences indicating persistence of globe configuration and optic nerve configuration for both resolved and active papilloedema groups. Timing may have also been an issue. The average time to resolution of papilloedema was 4.4 years and ranged from 8 months to 10 years (Table 1). It is possible that the

structural changes after ICP normalisation may no longer persist if MRI were performed further out from the resolution of the disease process.

It should also be noted that our control group also demonstrated some of the neuroimaging features of IIH, suggesting that these findings can be found to some degree in normal patients with no history of the disease and no papilloedema. This has been demonstrated previously³ and suggests that these imaging features exist on a continuum, and are not specific for IIH. Although we could not justify performing lumbar puncture in control group subjects, the complete lack of active or previous papilloedema and absence of any signs or symptoms of intracranial hypertension indicates normal ICP in this group.

In summary, we found that some of the characteristic neuroimaging features of IIH, specifically sellar and globe configuration, suggest a statistical trend for persistence after papilloedema has resolved and ICP has normalised. Careful clinical correlation and fundus examination are essential because some of these neuroimaging features can be seen in normal patients, and their presence on MRI does not necessarily indicate active disease or elevated ICP. Elevated ICP may cause persistent and possibly permanent structural changes in the optic nerve, brain, and CSF spaces, but the long-term implications of this finding remain unclear.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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