Brain MRI and ophthalmic biomarkers of intracranial pressure

Authors:

Linda D'Antona, MD, MBBS; Hasan Asif, MRCS; Claudia Louise Craven, M.Sc., MRCS; James Alexander McHugh, FRCOphth; Anna Vassiliou, B.Sc.; Lewis Thorne, FRCS Neurosurgery; Manjit Singh Matharu, PhD, FRCP; Laurence Dale Watkins, MD, FRCS Neurosurgery; Fion Bremner, PhD, FRCOphth; Ahmed Kassem Toma, MD, FRCS Neurosurgery

Affiliations:

Linda D'Antona, National Hospital for Neurology and Neurosurgery, Victor Horsley Department of Neurosurgery, London, UK and UCL Queen Square Institute of Neurology, London, UK

Hasan Asif, National Hospital for Neurology and Neurosurgery, Victor Horsley Department of Neurosurgery, London, UK

Claudia Louise Craven, National Hospital for Neurology and Neurosurgery, Victor Horsley Department of Neurosurgery, London, UK

James Alexander McHugh, King's College Hospital NHS Foundation Trust, Department of Ophthalmology, London, UK

Anna Vassiliou, National Hospital for Neurology and Neurosurgery, Victor Horsley Department of Neurosurgery, London, UK

Lewis Thorne, National Hospital for Neurology and Neurosurgery, Victor Horsley Department of Neurosurgery, London, UK

Manjit Singh Matharu, National Hospital for Neurology and Neurosurgery, Headache and Facial Pain Group, London, UK and UCL Queen Square Institute of Neurology, London

Laurence Dale Watkins, National Hospital for Neurology and Neurosurgery, Victor Horsley Department of Neurosurgery, London, UK and UCL Queen Square Institute of Neurology, London, UK

Fion Bremner, National Hospital for Neurology and Neurosurgery, Department of Neuro-Ophthalmology, London, UK and UCL Queen Square Institute of Neurology, London, UK

Ahmed Kassem Toma, National Hospital for Neurology and Neurosurgery, Victor Horsley Department of Neurosurgery, London, UK and UCL Queen Square Institute of Neurology, London, UK

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Corresponding author:

Dr Linda D'Antona

Box 32, Victor Horsley Department of Neurosurgery, The National Hospital for Neurology and Neurosurgery, Queen Square, London, UK, WC1N 3BG.

Phone: +4407462906272

Email: linda.d'antona@nhs.net

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ABSTRACT

Objective:

To evaluate the utility of brain MRI and ophthalmic biomarkers for the prediction of intracranial hypertension, we have studied the association between six biomarkers and 24-hour intracranial pressure (ICP) monitoring results in 45 patients.

Methods:

This single-centre observational study includes patients who underwent 24-hour ICP monitoring, brain MRI (within three months) and ophthalmic assessment (during ICP monitoring). Six biomarkers were investigated: pituitary gland shape, vertical tortuosity of the optic nerve, distension of the optic nerve sheath, optic disc protrusion (MRI), papilloedema (slit lamp biomicroscopy) and spontaneous venous pulsations (SVP, infrared video recordings).

Results:

Forty-five patients (mean age 39±14SD, 38 females) met the inclusion criteria. All 6 biomarkers had a significant association with 24-hour ICP. Concave pituitary gland was observed with moderately elevated median ICP. Protrusion of the optic disc (MRI), papilloedema and absence of SVP were associated with the highest median ICP values. Twenty patients had raised ICP (median 24-hour ICP>5.96 mmHg, cut-off obtained through Youden index calculation). Patients with all normal biomarkers had normal median ICP in 94% (St.Err.=6%) of the cases. All the patients with 3 or more abnormal biomarkers had intracranial hypertension. The combination of at least one abnormal biomarker in MRI and

ophthalmic assessments was highly suggestive of intracranial hypertension (AUC 0.94, 95% CI 0.93-0.94)

Conclusions:

Brain MRI and ophthalmic biomarkers can non-invasively guide the management of patients with suspected CSF dynamics abnormalities. Patients with multiple abnormal biomarkers (≥3) or a combination of abnormal MRI and ophthalmic biomarkers are likely to have intracranial hypertension and should be managed promptly.

INTRODUCTION

Intracranial pressure (ICP) is an important physiological parameter and its measurement assists clinicians in the diagnosis and management of a variety of diseases. To this date, ICP assessment still requires invasive methods including lumbar punctures and intraparenchymal ICP monitoring with intracranial bolts. Several non-invasive methods to detect intracranial hypertension have been suggested, however, none of these techniques has yet been able to replace invasive ICP measurements [1-3].

Brain MRIs and ophthalmic exams are non-invasive assessments commonly performed in elective patients with suspected raised ICP and are accessible in most non-emergency clinical settings. Brain MRI markers such as the shape of the pituitary gland, vertical tortuosity of the optic nerves and distension of the optic nerve sheath can be useful signs of raised ICP in patients with Idiopathic Intracranial Hypertension (IIH) [4-12]. In addition to the presence of papilloedema [13], the absence of spontaneous venous pulsations (SVP) on infrared videography has been shown to have a strong correlation with raised ICP and represents a good ophthalmic marker for the prediction of intracranial hypertension [14].

Previous studies have separately looked at ophthalmic or brain MRI correlates of ICP and in most cases relied on lumbar punctures for the measurement of ICP. To our knowledge this is the first study assessing both brain MRI and ophthalmic biomarkers of ICP in a population of patients undergoing elective 24-hour ICP monitoring for suspected cerebrospinal fluid (CSF) dynamics abnormalities. The primary objective of this study is to identify which biomarkers are associated with the highest levels of ICP, and the secondary objective is to determine which biomarkers have the best positive and negative predictive values for detecting elevated ICP.

METHODS

This is a single centre retrospective observational study conducted at the National Hospital for Neurology and Neurosurgery (London, UK).

Standard Protocol Approvals, Registrations, and Patient Consents

This study has been approved by the North East-Newcastle & North Tyneside 2 Research Ethics Committee and the Health Research Authority (20/NE/0127). Due to its retrospective nature, written consent was waived.

Participants

This study includes a consecutive series of patients investigated with elective 24-hour ICP monitoring in the period between January 2017 and February 2020. We searched our ICP monitoring database to identify patients meeting the following eligibility criteria: (i) investigated with elective 24-hour ICP monitoring for suspected CSF dynamics disorder (e.g. IIH, Chiari, hydrocephalus, spontaneous intracranial hypotension, shunt malfunction), (ii) brain MRI performed within 3 months of the ICP monitoring with no intervention performed in between events and (iii) ophthalmic examination performed by an ophthalmologist during the 24-hour ICP monitoring period including assessment of papilloedema (by slitlamp biomicroscopy) and SVP (by infrared video recordings) [14, 15].

ICP monitoring

The clinical indications for 24-hour ICP monitoring were routinely discussed within a multidisciplinary team including neurosurgeons, neurologists and ophthalmologists. ICP monitoring was performed according to an established standardised protocol [16, 17]. On the

morning of admission, the patients had a right frontal intraparenchymal ICP measuring sensor inserted in the operating theatre under local anaesthesia. High frequency ICP data (100 Hz) were collected for a continuous period of 24 hours. During the daytime monitoring period, patients were encouraged to mobilise to simulate their usual level of activity. At the end of the 24 hours, the ICP raw data were downloaded and processed through the software ICM+© (University of Cambridge, UK). This analysis resulted in a mean ICP value for each minute of recording (minute-by-minute results). The results were then summarised in terms of median ICP over the entire 24 hours. A detailed description of the 24-hour ICP monitoring procedure employed at our institution has previously been published [16, 17]. For the interpretation of the ICP monitoring results, it should be noted that patients considered to have 'normal' ICP monitoring results with this technique have previously been reported to have a median 24-hour ICP of 3.21 mmHg (95% CI 2.29–4.13) [16].

Brain MRI imaging assessment

Brain MRIs performed within 3 months of the ICP monitoring period were selected. The imaging evaluation was performed by two independent trained assessors (H.A. and C.L.C.) masked to the 24-hour ICP results. Discordances between the two assessors were settled through consensus. Four imaging markers were assessed and graded as binary variables (normal/abnormal): pituitary gland shape, vertical tortuosity of the optic nerves, protrusion of the optic disc and distension of the optic nerve sheath [7]. The pituitary gland shape was assessed according to the classification proposed by Yuh *et al.* in 2000 [10]. A concavity of the pituitary gland of more than 1/3 of the height of the sella was considered abnormal, this corresponds to categories III, IV and V of the Yuh classification system and includes both empty and partially empty sella (**Figure 1A**). Protrusion of the optic disc was confirmed when the sclera was concave at the point of attachment of the optic nerve with associated

intraocular protrusion of the disc (**Figure 1B**) [4, 12]. The vertical tortuosity of the optic nerve was defined as a 'S-shaped' appearance of the optic nerve on sagittal views (**Figure 1C**) [4]. Similarly, to Agid *et al.*, the optic nerve sheath was considered distended when the CSF in the subarachnoid space surrounding the optic nerve was wider than 2 mm at any point within the 10 mm behind the globe (**Figure 1B**) [4]. Distension of the optic nerve sheath, optic nerve sheath protrusion and vertical tortuosity of the optic nerve were classified as abnormal whether present unilaterally or bilaterally. T1-weighted sagittal MRI sequences were used to assess pituitary gland shape and vertical tortuosity of the optic nerves, while T2-weighted axial MRI sequences (non-fat-suppressed) were used to assess optic disc protrusion and optic nerve sheath distension.

Ophthalmic Assessment

Ophthalmic assessments were performed during the 24-hour ICP monitoring period and included: slit lamp assessment of papilloedema (Frisén grading), intraocular pressure (IOP) and motion-stabilised SVP infrared videography. Papilloedema was defined as Frisén grade 2 or greater during slit lamp exam in at least one eye. The SVP videos were graded by two independent assessors (J.A.M. and F.B.) according to the grading system proposed by Hedges *et al.* [18]. The two assessors were masked to the ICP results. Absence of SVP was defined as grade 0 SVP bilaterally as judged by both the assessors. Further details on the methods of assessment and interpretation of SVP were previously published [14, 15].

Statistical analysis

Association between biomarkers and ICP

The mean 24-hour ICP of the patients with normal and abnormal biomarkers were compared (Mann-Whitney U test). The strength of the association between ICP and the 6 biomarkers

was evaluated through Receiver Operating Characteristic (ROC) curves and Areas Under the Curves (AUC). The strength of the associations was defined as acceptable (AUC 0.7 to 0.8), excellent (AUC 0.8 to 0.9) or outstanding (AUC >0.9) [19]. Frequency distribution analyses were used to describe the time-ICP burden for each biomarker and identify the biomarkers associated with the highest (and lowest) level of ICP. ROC and frequency distribution analyses were performed using the patients' minute-by-minute ICP monitoring results (about 1440 mean 1-minute ICP values per patient).

Predictive value of the 6 biomarkers

A ROC curve analysis using mean minute-by-minute ICP data (predictor) and normal versus abnormal biomarkers (binary classifier) was performed to identify the optimal median 24-hour ICP cut-off (Youden index). The positive and negative predictive values (PPV and NPV) of the biomarkers in identifying intracranial hypertension were calculated.

Due to the exploratory and retrospective nature of the study a formal sample size calculation was not performed and all eligible patients were identified and included in the study.

Continuous variables were summarised as means (standard deviation) and categorical variables as percentages. A significance level 0.05 was used. Microsoft® Excel for Mac (version 16.25), Stata© (version 15.0) and GraphPad Prism for macOS (version 8.4.1) were used for the data collection and statistical analysis.

Data availability statement

Anonymized study data for the primary analyses presented in this report are available on request from any qualified investigator for purposes of replicating the results.

RESULTS

Participants

Between January 2017 and February 2020, 400 patients underwent elective continuous 24-hour ICP monitoring. Forty-five patients met the eligibility criteria and were included in the study. The baseline demographic characteristics, indications for 24-hour ICP monitoring, results of ICP monitoring, brain MRI features and ophthalmology findings are summarised in **Table 1**. The average interval time between brain MRI and 24-hour ICP monitoring was 36 (SD 31) days, while all ophthalmology exams were performed during the ICP monitoring period.

ICP monitoring results

Table 2 and **Figure 2** describe the mean (SD) ICP results of the patients stratified by imaging and ophthalmic findings. 24-hour ICP results were significantly higher in patients with abnormal biomarkers compared to patients in whom the markers were normal (Mann-Whitney U, $p<0.05$ in all 6 analyses, **Table 2**).

Biomarkers and their association with ICP

The minute-by-minute patients' ICP values (70,467 observations) were extracted and plotted in frequency distribution graphs stratified by biomarker results (**Figure 3**).

Association of brain MRI biomarkers and ICP

Patients with concave pituitary gland (or empty sella) had a median ICP of 10 mmHg (**Figure 3**), this value indicates intracranial hypertension but is lower if compared to the other abnormal biomarkers. Protrusion of the optic disc detected on MRI imaging was associated with higher ICP levels and the 4 patients with this sign had a median ICP of 24 mmHg

(**Figure 3**). ROC curve analyses showed that ICP measurements (minute-by-minute) had an outstanding association (AUC > 0.90) with optic disc protrusion detected on MRI imaging (AUC=0.94, 95% CI 0.93-0.94). The associations with ICP (minute-by-minute) were excellent (AUC between 0.8 and 0.9) for vertical tortuosity of the optic nerves (AUC=0.82, 95% CI 0.81-0.82) and pituitary gland shape (AUC=0.80, 95% CI 0.79-0.81). The association with ICP (minute-by-minute) was acceptable (AUC between 0.70 and 0.80) for the distension of the optic nerve sheath (AUC=0.75, 95% CI 0.74-0.75).

Association of *ophthalmic biomarkers and ICP*

Patients with absence of SVP (n=10) had a median ICP of 19 mmHg and patients with papilloedema (n=2) or had a median ICP of 24 mmHg (**Figure 3**). The minute-by-minute ICP had an excellent association (AUC between 0.80 and 0.90) with both papilloedema (AUC=0.90, 95% CI 0.90-0.91) and absence of SVP (AUC=0.85, 95% CI 0.84-0.85).

Positive and negative predictive value of the 6 biomarkers

Sixteen patients (36%) in this study had no abnormal biomarkers on MRI or ophthalmic examination. The mean 24-hour ICP in this subgroup of patients was 2.7 mmHg (SD 5.6). The ROC curve analysis identified 5.96 mmHg as the optimal median 24-hour ICP threshold distinguishing patients with normal biomarkers from patients with 1 or more abnormal biomarkers (based on Youden index calculation).

The biomarker with the best negative predictive value was the pituitary gland shape; a normal pituitary gland shape predicted normal ICP (median 24-hour ICP < 5.96 mmHg) in 86% of the cases. The biomarkers with the best positive predictive values were SVP, papilloedema and protrusion of the optic disc; if abnormal these markers identified raised ICP (median 24-hour ≥ 5.96 mmHg) in 90%, 100% and 100% of the study patients respectively.

ICP was elevated (median 24-hour ICP > 5.96 mm Hg) in 6% of patients with no abnormal markers, 46% of patients with 1 abnormal marker, 50% of patients with 2 abnormal markers, and 100% of patients with 3 or more abnormal markers.

A comparison of brain MRI and ophthalmic biomarkers domains

Among the 45 patients, 28 had at least 1 abnormal biomarker in the brain MRI domain, 10 had at least 1 abnormal biomarker in the ophthalmic domain and 9 had at least 1 abnormal biomarker in each of the 2 domains (brain MRI and ophthalmic). Patients with at least one abnormal biomarker in the brain MRI domain had a median ICP of 9.4 mmHg, while patients with at least 1 abnormal biomarker in the ophthalmic domain had a median ICP of 18.9 mmHg (**Figure 5A and B**). Patients with at least one abnormal biomarker in each of the two domains had the highest median ICP (20.7 mmHg, **Figure 5C**). The combination of one abnormal biomarker in each of the two domains achieved the strongest association with ICP (AUC 0.94, 95% CI 0.93 to 0.94, **Figure 5D**).

DISCUSSION

This observational study describes the association of ICP with brain MRI and ophthalmic biomarkers of intracranial hypertension in a group of 45 patients with suspected CSF dynamics disorders. Our predictive values analysis demonstrated that patients with 3 (or more) abnormal biomarkers invariably had high median 24-hour ICP (100% PPV). Patients without any abnormal biomarker had normal ICP in 94% of the cases. There was only 1 patient with raised ICP and normal biomarkers, he had a median 24-hour ICP of 6.5 mmHg, this value is very close to the optimal ICP cut-off considered for this analysis.

Patients with optic disc protrusion identified with brain MRI, papilloedema and/or absence of SVP on infrared videography had higher ICP levels compared to patients with other abnormal biomarkers (**Figure 3**). A concave pituitary gland (or empty sella) was associated with the lowest ICP levels. This may represent an earlier marker of elevated ICP than other biomarkers, although this study's design did not permit this hypothesis to be directly tested. The simultaneous presence of at least one abnormal marker in the brain MRI domain and at least one abnormal marker in the ophthalmic domain achieved the strongest association with ICP readings (AUC 0.94, 95% CI 0.93 to 0.94, **Figure 5D**).

For ethical reasons, continuous ICP monitoring has not been performed in healthy subjects, therefore there is uncertainty about the level of median 24-hour ICP that can be considered normal. Our calculation of an optimal ICP cut-off is not intended as a definition of normal/abnormal ICP values, but rather as the ICP threshold above which increased ICP became increasingly associated with MRI and ophthalmic biomarkers of intracranial hypertension in a group of patients undergoing clinically indicated investigations. As most physiological parameters, we expect ICP to vary among different people and a normal ICP to

be best defined by ranges rather than a specific cut-off value. Moreover, this value was obtained from a population of patients who had a clinical indication for ICP monitoring, therefore they cannot be considered representative of a completely healthy population. However, this calculation was necessary for the evaluation of the utility of the 6 biomarkers in clinical practice. Interestingly, the cut-off obtained with this analysis is very close to the 'normal' ICP previously obtained by Chari *et al.* through the principal component analysis of a large group of patients undergoing 24-hour ICP monitoring [16].

Bilateral stenosis of the transverse sinuses on post gadolinium brain MRI has been reported to have the highest sensitivity for the diagnosis of IIH among other imaging biomarkers [20]. Due to the lack of availability of MRI with contrast (not routinely performed for this patient cohort in our institution) and to the heterogenous indications for ICP monitoring (not only IIH) of this patients' cohort, this sign could not be assessed in this study. However, it should be considered for the assessment of patients with IIH and in the design of future prospective studies. Patterson *et al.* suggested that the ability to non-invasively predict ICP is improved by multimodal assessment combining an orbital ultrasound measurement of optic nerve sheath diameter and MRI pituitary-to-sella ratio [21]. Compared to other previous studies investigating the role of brain MRI markers as predictors of ICP where 'snapshot' ICP estimates were made by lumbar puncture, our study has the advantage of relying on continuous ICP monitoring data [4-10]. This allowed us to achieve a better overview of the time-ICP burden in each patient group (**Figure 3**). The limitations of lumbar puncture opening pressures in this context have been previously exposed by Tuncel *et al.* who did not find any correlation between lumbar puncture opening pressures and imaging markers of intracranial hypertension [22].

Another important difference compared to previous studies is the inclusion of patients undergoing ICP monitoring for a variety of clinical indications, not only IIH (**Table 1**). Whilst this heterogeneity within the studied cohort may increase the 'noisiness' of the data, it does allow us to draw useful conclusions not only for IIH patients, but for any patient with suspected intracranial hypertension in a non-emergency setting.

An important limitation of this study is the fact that, while ophthalmic assessments were performed during the ICP monitoring period, brain MRIs were conducted at an average interval time of 36 days from the 24-hour ICP monitoring. The resulting risk of bias was addressed by only selecting patients who did not have any change in clinical picture or any type of intervention (including conservative treatments) in between the two events. It is unlikely that a clinical change would go unnoticed as patients attend multiple perioperative clinical appointments around the time of ICP monitoring and are encouraged to report any clinical change to the care team through a dedicated telephone line (and/or email address). Additionally, it should be noted that for 37 patients (82%) the brain MRI was performed before the ICP monitoring procedure. At our institution, patients who undergo ICP monitoring are those in whom there is diagnostic uncertainty and would not be treated solely on the basis of brain MRI imaging before confirmation of intracranial hypertension. The remaining eight patients had a brain MRI performed after the ICP monitoring as well as baseline brain imaging (either CT or MRI) performed before the time of ICP monitoring. For the purpose of the study, when multiple eligible brain MRIs were available, the imaging closer to the time of ICP monitoring was selected. The association between ICP and biomarkers was similar when comparing these eight patients to the rest of the cohort.

There are other limitations to this study. First of all, both ophthalmic and brain MRI imaging assessments are operator-dependent; however, there were two trained independent observers for each assessment, and they were masked to the ICP results at all times. The retrospective design of the study is another obvious limitation. A prospective study would have permitted the reduction of the interval between the investigations and to recruit a larger group of patients. Additionally, a prospective design would have resulted in the possibility of including different types of brain MRI sequences reported to be helpful in the literature. For example, our brain MRI assessment of the optic nerve features was not performed on fat-suppressed sequences. Fat-suppressed sequences can facilitate the assessment of the optic nerve sheath diameter, but they are not mandatory [7, 23]. This type of sequence was not available for most of the patients in this study as not routinely performed. Whilst it is possible that the predictive value of this marker would improve with the use of fat-suppressed MRI sequences, the visualisation of the optic nerve sheaths was deemed satisfactory by both the assessors for all the included MRIs. Finally, it is important to consider that ICP is affected by body position and while slit lamp examination and OCT scans are performed with the patient upright, MRIs are performed in the supine position [24, 25]. We have partially addressed this issue by using continuous 24-hour ICP monitoring readings as these will include ICP values measured in both body positions. These are the conditions (supine MRI and upright ophthalmic assessments) in which outpatients are routinely investigated for suspected abnormalities of ICP, and the significance of abnormal biomarkers observed in these positions is therefore relevant to real-world clinical practice.

Future research could improve our understanding on the utility of these biomarkers as predictors of intracranial hypertension by conducting large, prospective studies and should investigate the specificity of the MRI biomarkers in a large population of healthy controls.

CONCLUSIONS

MRI biomarkers of elevated ICP (arachnoid herniation into the sella, a distended optic nerve sheath, vertical optic nerve tortuosity, and optic disc protrusion) and ophthalmic biomarkers (absent spontaneous venous pulsation on infrared fundus video, disc swelling) are strongly associated with higher intracranial pressure. Patients with multiple abnormal biomarkers (≥3) or a combination of abnormal MRI and ophthalmic biomarkers are likely to have intracranial hypertension, therefore patients presenting this characteristic should be managed promptly.

Appendix 1. Authors

Name	Location	Contribution
Linda D'Antona, MD, MBBS	NHNN, London, UK	Designed and conceptualized study; acquired the data; analysed the data; interpreted the data; drafted the manuscript for intellectual content
Hasan Asif, MRCS	NHNN, London, UK	Designed and conceptualized study; acquired the data; interpreted the data; revised the manuscript for intellectual content
Claudia Louise Craven, M.Sc., MRCS	NHNN, London, UK	Designed and conceptualized study; acquired the data; interpreted the data; revised the manuscript for intellectual content
James Alexander McHugh, FRCOphth	King's College Hospital NHS Foundation Trust, London, UK	Acquired the data; interpreted the data; revised the manuscript for intellectual content
Anna Vassiliou, B.Sc.	NHNN, London, UK	Acquired the data; revised the manuscript for intellectual content
Lewis Thorne, FRCS Neurosurgery	NHNN, London, UK	Interpreted the data; revised the manuscript for intellectual content
Manjit Singh Matharu, PhD, FRCP	NHNN, London, UK	Interpreted the data; revised the manuscript for intellectual content
Laurence Dale Watkins, MD, FRCS Neurosurgery	NHNN, London, UK	Interpreted the data; revised the manuscript for intellectual content
Fion Bremner, PhD, FRCOphth	NHNN, London, UK	Acquired the data; interpreted the data; revised the manuscript for intellectual content
Ahmed Kassem Toma, MD, FRCS Neurosurgery	NHNN, London, UK	Designed and conceptualized study; interpreted the data; revised the manuscript for intellectual content
NHNN: National Hospital for Neurology and Neurosurgery		

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563 **Table 1.** Baseline patients' characteristics

Demographic characteristics	
Age, mean (SD)	39 (14)
Sex, n (%)	
- Females, n (%)	38 (84)
- Males, n (%)	7 (16)
Clinical indications for 24-hour ICP monitoring	
- Suspected CSF dynamics disorder causing headache (e.g. IIH, SIH)	22 (49)
- Suspected CSF shunt malfunction	12 (27)
- Hydrocephalus	7 (16)
- Chiari malformation	3 (7)
- Suspected NPH	1 (2)
ICP monitoring results in mmHg	
- 24-hour ICP, mean[a] (SD)	7.8 (8)
Brain MRI results	
- Concave pituitary gland or empty sella, n (%)	24 (53)
- Optic nerve sheath distension, n (%)	15 (33)
- Vertical tortuosity of optic nerves, n (%)	13 (29)
- Protrusion of the optic disc, n (%)	4 (9)
Ophthalmology results	
- Absence of SVP, n (%)	10 (22)
- Papilloedema, n (%)	2 (4)
- IOP in mmHg, mean[b] (SD)	15.3 (3)

[a] Mean of the patients' median results; [b] Mean of all eyes.

CSF: Cerebrospinal Fluid; ICP: Intracranial Pressure; IIH: Idiopathic Intracranial Hypertension; SD: Standard Deviations; SIH: Spontaneous Intracranial Hypotension; SVP: Spontaneous Venous Pulsation

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565 **Table 2.** Intracranial pressure monitoring results (in mmHg) stratified by imaging and
566 ophthalmic biomarkers

	Normal marker	**Abnormal marker**	**P value[b]**
Pituitary gland shape	N=21	N=24	
- 24-hour ICP, mean[a] (SD)	2.4 (3.4)	12.6 (8.1)	<0.001
Optic nerve sheath distension	N=30	N=15	
- 24-hour ICP, mean[a] (SD)	4.7 (5.7)	14.0 (8.9)	<0.001
Vertical tortuosity of optic nerves	N=32	N=13	
- 24-hour ICP, mean[a] (SD)	4.6 (5.9)	15.9 (7.4)	<0.001
Protrusion of the optic disc	N= 41	N= 4	
- 24-hour ICP, mean[a] (SD)	6.2 (6.5)	24.2 (4.3)	0.002
Spontaneous venous pulsation	N=35	N=10	
- 24-hour ICP, mean[a] (SD)	4.7 (4.1)	18.9 (9.1)	<0.001
Papilloedema	N=43	N=2	
- 24-hour ICP, mean[a] (SD)	7.1 (7.4)	23.1 (9.6)[c]	0.04

[a] Mean of the patients' median results; [b] Mann-Whitney U test; ICP: Intracranial Pressure;
[c]The individual median 24-hour ICP monitoring results for the 2 patients with papilloedema were 16.3 and 29.9 mmHg.

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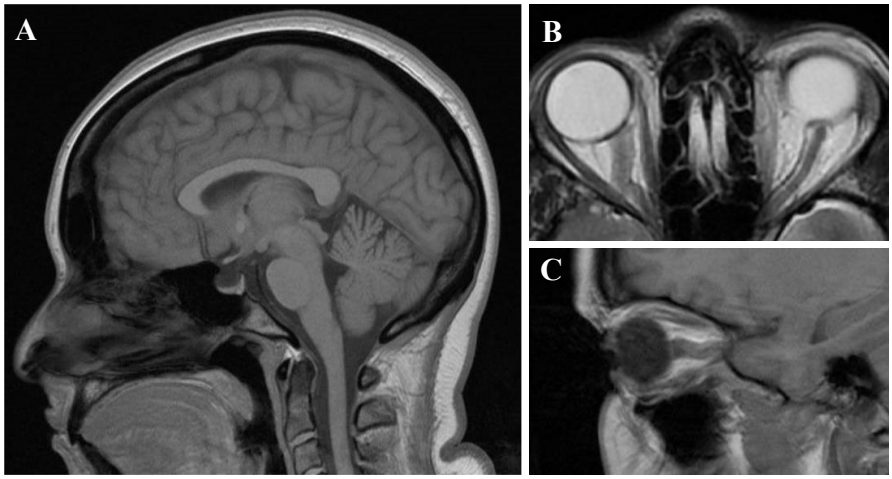
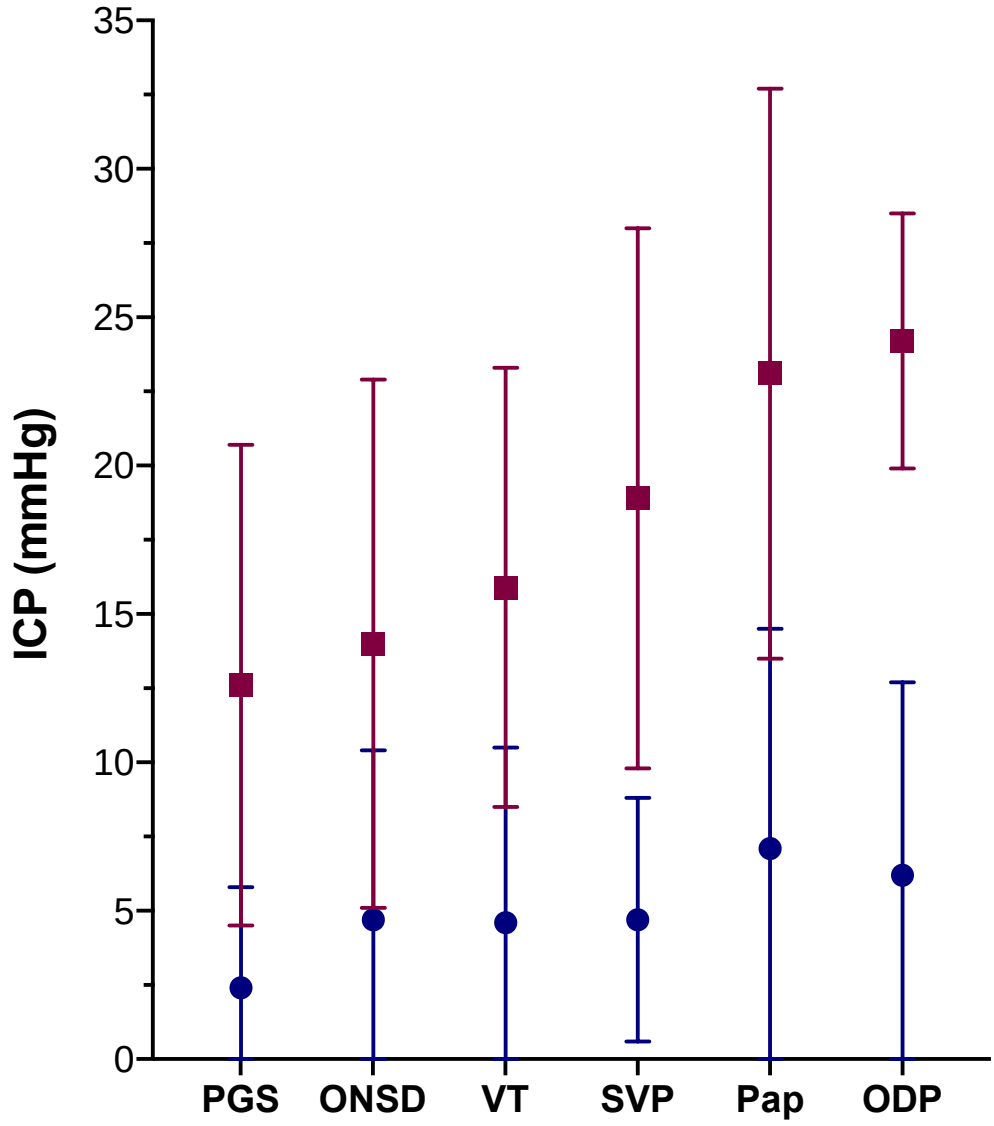
FIGURES

Figure 1. Example of the brain MRI biomarkers of intracranial hypertension. (A) T1-weighted sagittal brain MRI showing a partially empty sella; (B) T2-weighted axial brain MRI showing protrusion of the left optic nerve head and optic nerve sheath distension; (C) T1-weighted sagittal brain MRI showing vertical tortuosity of the optic nerve.



578 **Figure 2.** Mean (SD) intracranial pressure (ICP) stratified by normal and abnormal
579 biomarkers.



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581 *ICP: Intracranial Pressure, PGS: Pituitary Gland Shape, ONSD: Optic Nerve Sheath*
582 *Distension, VT: Vertical Tortuosity of the Optic Nerves, SVP: Spontaneous Venous Pulsation,*
583 *Pap: Papilloedema, ODP: Optic Disc Protrusion.*

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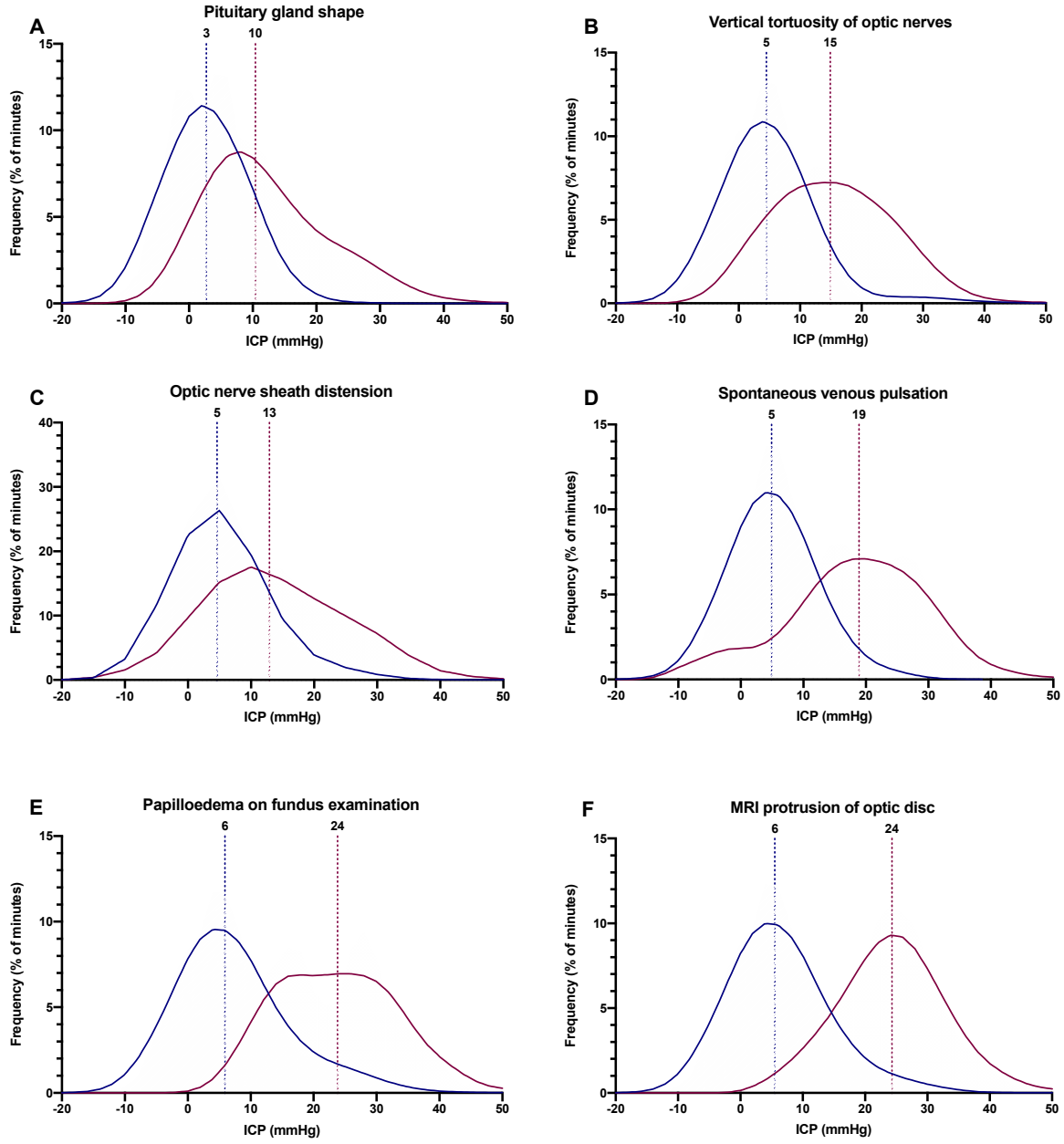
Figure 3. Frequency distribution of minute-by-minute Intracranial Pressure (ICP) of patients presenting normal (blue) and abnormal (red) biomarkers.



LOWESS smoothing line and median ICP are marked.

Figure 4. Receiver Operating Characteristic (ROC) curves and Areas Under the Curves (AUC) representing the association of Intracranial Pressure (ICP) with the biomarkers. (A) Brain MRI biomarkers: pituitary gland shape (PGS, AUC=0.80), Vertical Tortuosity of the optic nerves (VT, AUC= 0.82), Optic Nerve Sheath Distension (ONSD, AUC= 0.75), Optic Disc Protrusion (ODP, AUC=0.94); (B) Ophthalmic biomarkers: papilloedema (Pap, AUC=0.90), Spontaneous Venous Pulsation (SVP, AUC= 0.85).

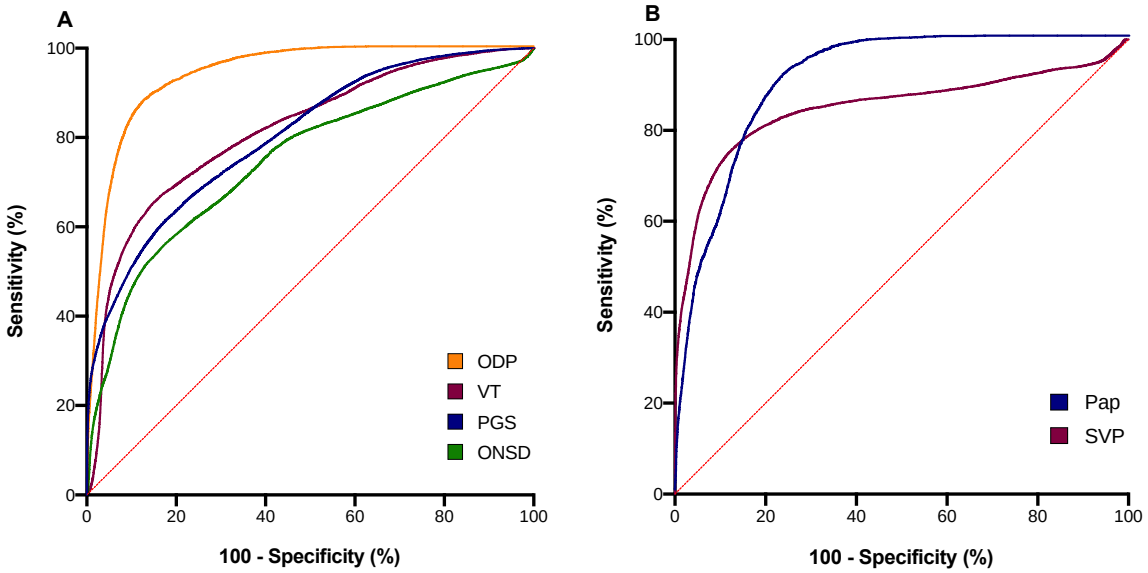


Figure 5. Subgroup analysis by brain MRI and ophthalmic domains. (A-C) Frequency distribution of minute-by-minute Intracranial Pressure (ICP) of patients presenting normal (blue) and abnormal (red) biomarkers. (D) Receiver Operating Characteristic (ROC) curves representing the association of ICP with the biomarkers classified by domains (brain MRI and ophthalmic).