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Observational study of intracranial pressure instability in patients with pseudotumour cerebri syndrome

Afroditi D. Lalou [a,b,c,*], Zofia H. Czosnyka [a], Marek Czosnyka [a]

[a] Department of Clinical Neurosciences, Division of Neurosurgery, Brain Physics Laboratory, University of Cambridge & Cambridge University Hospital NHS Foundation Trust, United Kingdom
[b] Department of Neurology, King's College Hospital NHS Foundation Trust, London, United Kingdom
[c] Department of Radiation Sciences, Faculty of Medicine, Umeå University, Umeå, Sweden

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ABSTRACT

Introduction: A fixed CSF pressure (CSFp) of 25 cmH2O (18 mmHg) has been utilised to date to define and classify pseudotumour cerebri syndrome (PTCS). Furthermore, ICP monitoring, and CSF infusion tests have not been frequently performed in this group of patients.
Research question: We aimed to report typical, unusual and unstable patterns of ICP in patients with PTCS.
Material and methods: We reviewed the recordings of CSF infusion tests and overnight ICP monitoring of patients with suspected or confirmed IIH between January 2003–December 2020.We excluded all patients with a shunt in situ and selected recordings that represented unstable patterns of ICP changes in PTCS.
Results: 463 CSF infusion tests and 26 ICP monitorings of PTCS patients had been performed in this timeframe. We divided results of observed pattern into two group: those with known venous sinus measurements (Group A) and those without (Group B). Observed recordings formed a total of 5 and 4 different patterns respectively, based on the behaviour of ICP and slow waves at rest, overnight, and during infusion as well as in relationship to the clinical presentation of each patient.
Discussion and conclusion: Accurate monitoring of ICP in PTCS is quintessential. Full understanding of each element of its pathophysiology and their interaction would be essential and include quantification of the CSF pressure not only as a number, but also with consideration of its dynamic contents. Cerebral venous pressure measurements and/or monitoring may be useful. Consideration of the presence or absence of papilloedema in the context of disturbed CSF dynamics could reveal further diagnostic and therapeutic insights.

1. Introduction

Pseudotumour cerebri syndrome (PTCS) has received several names and descriptions as our understanding of the disorder advanced through the years. In this observational study we use PTCS to describe the entirety of the syndrome, including all its described causes, especially abnormalities of the cerebral venous outflow. Idiopathic In contrast, Idiopathic Intracranial Hypertension (IIH) includes only the cases with no causal or pathophysiological link. It is generally perceived as a disorder of post-pubertal females with raised BMI; however, male, lean and paediatric patients can be also affected at a non-negligible percentage (Lalou et al., 2020a; Andrews et al., 2014; Matthews et al., 2017; Friedman and Liu, 2013; McTaggart et al., 2020).

Another current perception is the use of a single LP manometry to define a "normal threshold" that confirms, probates, or negates the diagnosis of PTCS (Friedman and Liu, 2013; Dandy, 1937; Moavero et al., 2018). Current intracranial pressure (ICP) thresholds promote 25cmH2O (roughly 18.5 mmHg) for adult as well as paediatric non obese and non-sedated patients and 28cmH2O (20.6 mmHg) for obese and/or sedated children (Friedman and Liu, 2013; Avery et al., 2010; Olesen et al., 2013). The rarity and complexity of the disorder has led to a sparsity of critical reviews and standardisation of ICP measurement methodology (Cartwright and Igbaseimokumo, 2015; Lewis et al., 2012; Czosnyka et al., 1988, 2004, 2007a, 2007b; García et al., 2013; Balestreri et al., 2004; Cardim et al., 2016a; Kasprowicz et al., 2016; Czosnyka, 2013; Donnelly et al., 2018). Furthermore, diagnosis and treatment are hindered by a lack of pathophysiological understanding and hence lack of individualised treatment targets to successfully

* Corresponding author. Department of Radiation Sciences, Umeå Universitet, Umeå, Sweden.
E-mail address: afroditi.lalou@umu.se (A.D. Lalou).

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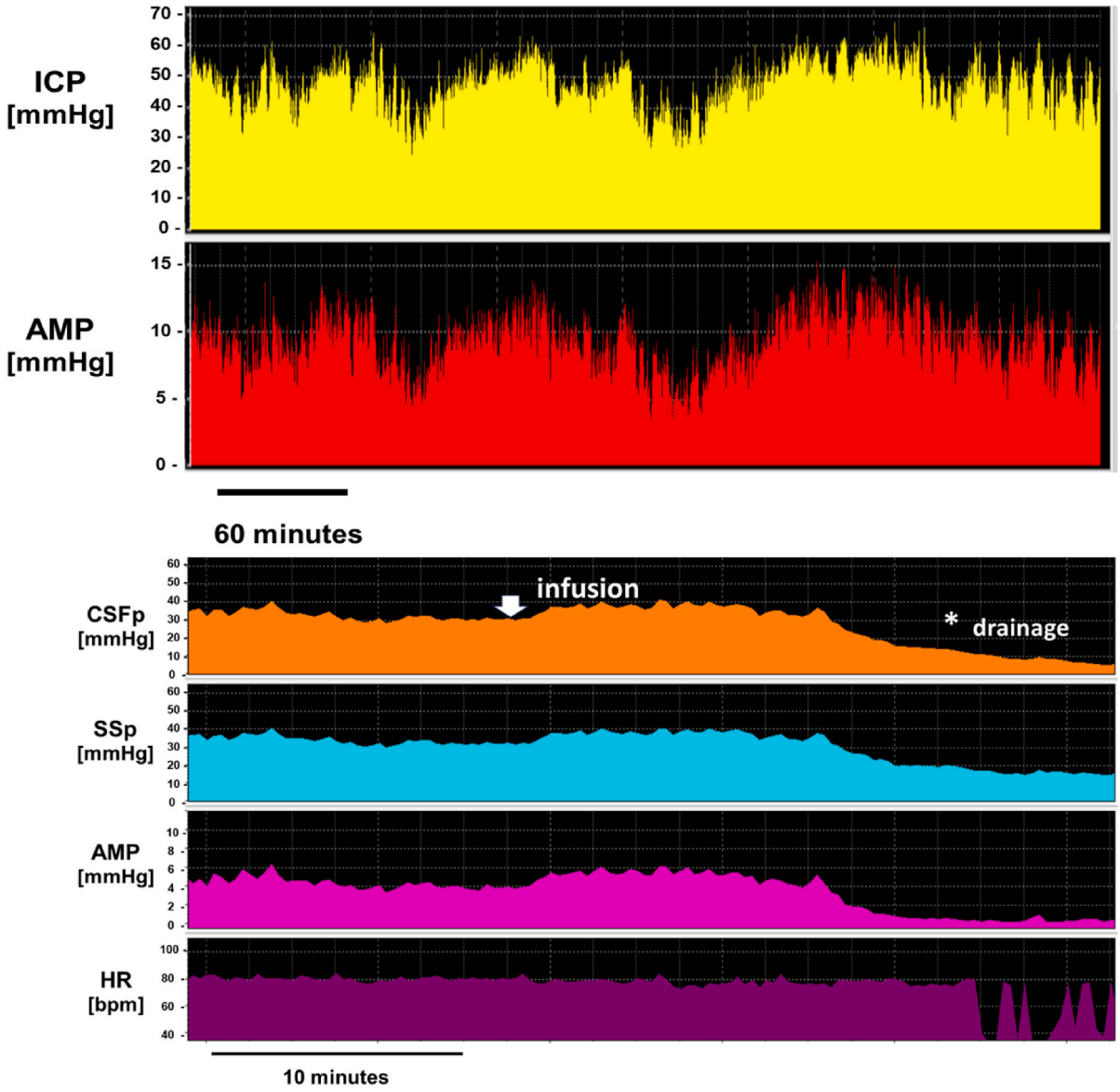


Fig. 1. Patients with PTCS and stable ICP. Upper panel: Increased ICP overnight, in the range of 30–40 mmHg and stable. Lower panel: Cerebrospinal Fluid Infusion test of a patient with Idiopathic Intracranial Hypertension (PTCS, no cause identified). Stable & elevated CSFp at baseline (22 mmHg), with mild increase in CSFp during infusion (up to 30 mmHg). *ICP: Intracranial Pressure. AMP: fundamental amplitude of ICP.*

address the disease burden.

Over the years, we have accumulated experience with several different PTCS phenotypes and pressure recordings. We aimed to summarise the different clinical & CSF dynamics findings of the patients investigated in our centre to assess the heterogeneity of the disease spectrum.

2. Material and Methods

2.1. Assessing cerebral circulation: CSF infusion tests and ICP monitoring

We have described the constant-rate infusion test methodology used in our lab in several other publications (García et al., 2013; Czosnyka et al., 1996, 2005; Smielewski et al., 2005; Eisenträ et al., 2013; Børgesen et al., 1992; Bech-Azeddine et al., 2005; Sundström et al., 2010; Katzman and Hussey, 1970; Andersson et al., 2008; Lalou et al., 2020b). Infusion tests are performed via LP or a pre-implanted access device under a standardised local protocol, that has remained the same since 2001. In brief, after access to the CSF space is confirmed, the CSFp signal is transduced to a monitor and recorded in our software (Smielewski et al., 2005, 2008). CSFp is monitored for at least 15 min, ensuring that it is stable after connection and allowing for calculation of compensatory parameters. Infusion of Saline or Hartmann's is started (for PTCS patients the infusion rate is 1.0 ml/min, as the baseline CSFp almost always exceeds 13 mmHg). A safety threshold of 40 mmHg is set so that, if exceeded, infusion is stopped. If the CSFp does not recover within a few seconds to minutes, safety drainage is performed. At times, large amplitude slow-waves (b-waves) can develop, with amplitude <50 mmHg and duration <1 min that oscillate and are safe for the patient, unlike the larger-amplitude plateau waves (not observed in any of our PTCS patients, as they are usually a result of cerebral vasodilation). Slow drainage of 30–50 mls of CSF, depending on how each patient tolerates it, is performed at the end of each test.

Over the years, we have performed several hundreds of CSF infusion tests and a few overnight ICP recordings of PTCS patients that have revealed several pathophysiological insights into the disorder.

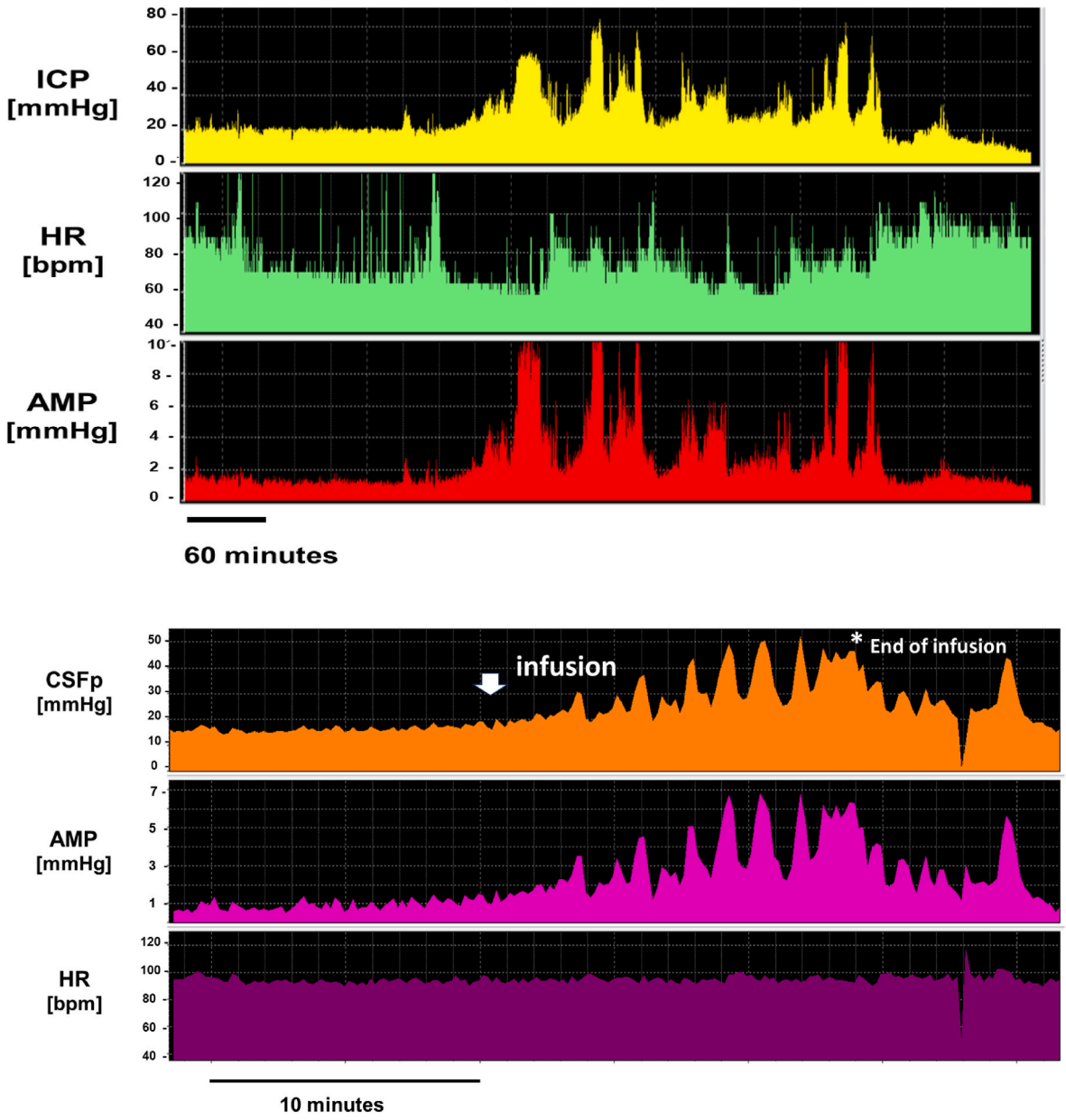


Fig. 2. Patients with PTCS, with high variation in ICP range. Upper panel: Initial ICP before sleep was 20 mmHg, followed by overnight waves of 60–70 mmHg during sleep, then 10 mmHg during awake state. Lower panel: Stable & "borderline" elevated CSFp at baseline (18 mmHg), with high amplitude vasogenic waves >50 mmHg appearing during infusion. *ICP: intracranial pressure, HR: heart rate, AMP: fundamental amplitude of ICP.*

2.2. Grouping of observed patterns

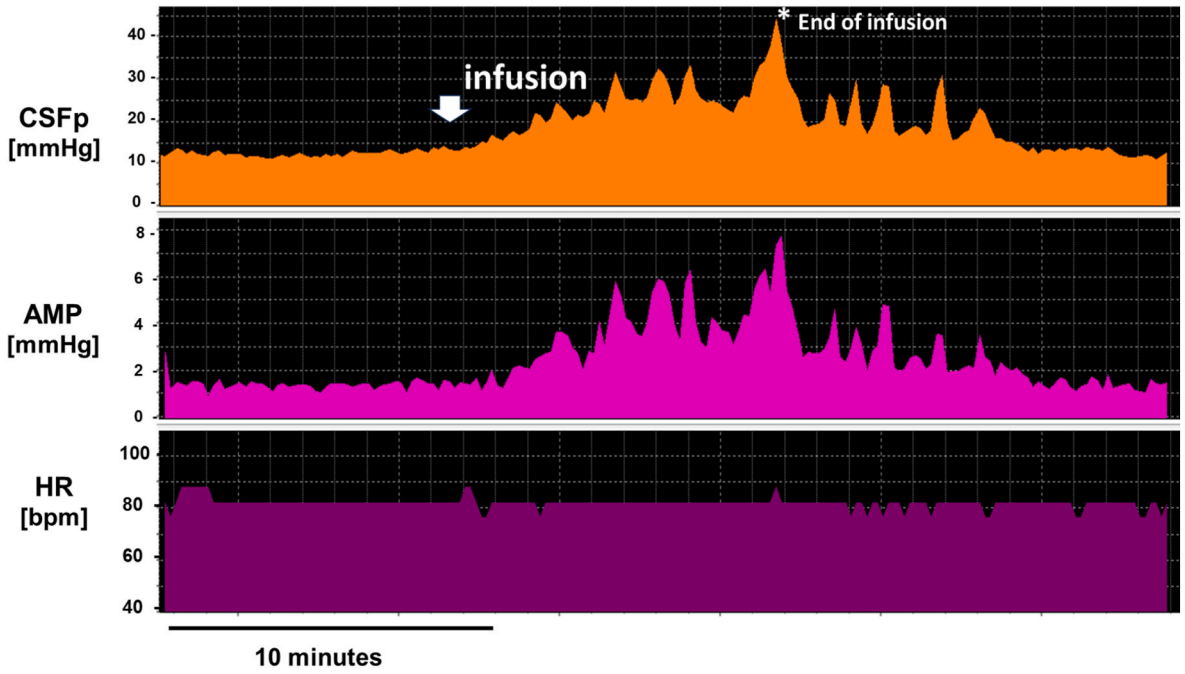
We examined all recordings from January 2003 to December 2020. We excluded patients with a working shunt or venous stent in situ and selected patterns of ICP changes in PTCS that showed significant variation in CSF dynamics.

We aimed to solely identify all observed variations in ICP, regardless of how frequently these were observed. As such, we synthesised an illustrative account of the patterns observed without a numerical analysis and without summary statistics. We elected to perform a visual classification rather than any quantitative or statistical grouping, for 3 main reasons.

1. Visual exploration is essential as a first step for our recordings, to ensure accuracy of the extracted values, validity of the recording and absence of artefacts/interruptions to the test.
2. Averaging numbers of recordings will not allow for accurate exploration of the changes and fluctuations seen in most overnight ICP recordings and CSF infusion test recordings (e.g. b-waves, intervals of lower and higher ICP
3. Defining any numerical thresholds that would be directly clinically useful was not within the scope of this study. Translating our current observations into further understanding of the disorder, diagnostic testing and interpretation of CSF infusion test results should be further explored in large prospective studies, with comparison of current diagnostic consensus undertaken.

We inspected for the following features: A) The range and behaviour of ICP/CSFp. B) Whether any fluctuations in ICP were due to ICP waves (plateau waves or slow waves) or due to a separate phenomenon. C) the relationship with any recorded cerebral venous sinus pressure D) The documented presence or absence of optic disc oedema.

"Stable" ICP was determined as any infusion or overnight ICP that



Pattern 3. IIH – increased CSFp during infusion only. Example of a patient with a clinical diagnosis of IIH, showing an opening CSFp at 10 mmHg, with a steep rise during infusion to 45 mmHg with slow wave activity.

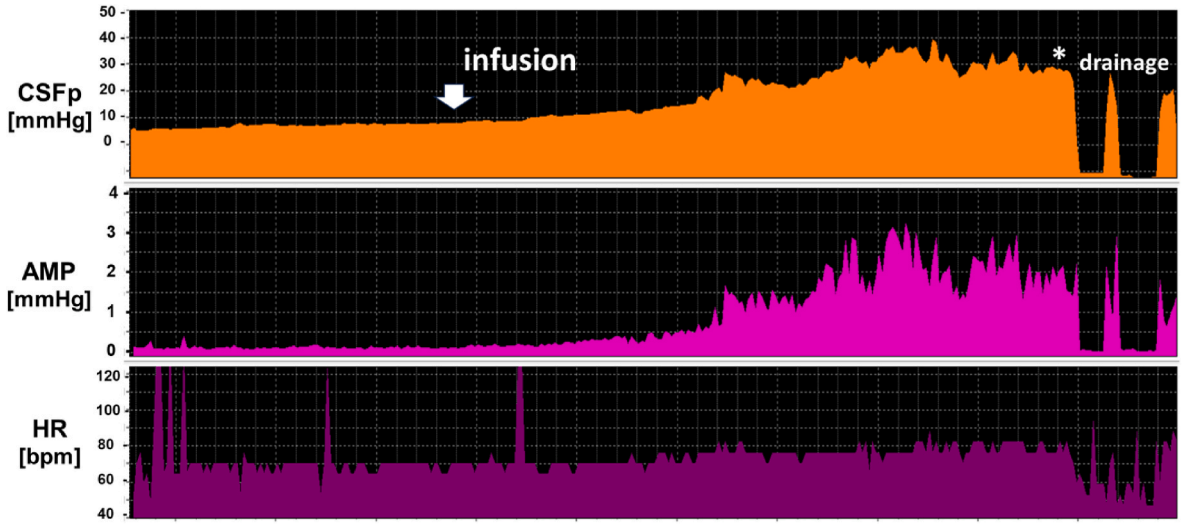


Fig. 4. Cerebrospinal Fluid Infusion test in patient with Idiopathic Intracranial Hypertension (PTCS, no cause identified).

demonstrated no or very limited fluctuation (<5 mmHg). "Unstable" ICP was determined as any fluctuation in ICP/CSFp at baseline, during infusion or during the overnight recording.

"Elevated" ICP was >18 mmHg, as per consensus of 25cmH2O (Friedman and Liu, 2013). Ranges of 15–18 mmHg were considered as "normal" or "normal to borderline".

3. Results

There were 29 overnight ICP monitoring and 436 CSF infusion test recordings of IIH patients. We identified two main categories of patients investigated: Group A included patients without any documented recording of the venous sinus pressures. Group B included patients where there was direct or indirect measurement and/or recording of venous sinus pressures (N = 11).

Group A: ICP/CSF pressure recordings without knowledge of the venous sinus pressure.

3.1. Long-term ICP monitoring. How stable ICP is in PTCS patients

From overnight ICP monitoring, the first pattern that we observed was raised, stable ICP (>20 mmHg). This example is illustrated in Fig. 1, upper panel.

3.2. CSF infusion tests: baseline pressure and pressure during infusion

In CSF infusion tests, we observed stable baseline CSFp (≥20 mmHg), that did not increase significantly with infusion studies (Fig. 1, lower panel). There were a few cases on opposite ends of the spectrum: On one end, the CSF pressure increased significantly more than expected (Fig. 2), with strong vasogenic waves appearing during infusion.

Not all patients exhibited the same stability in ICP overnight. We

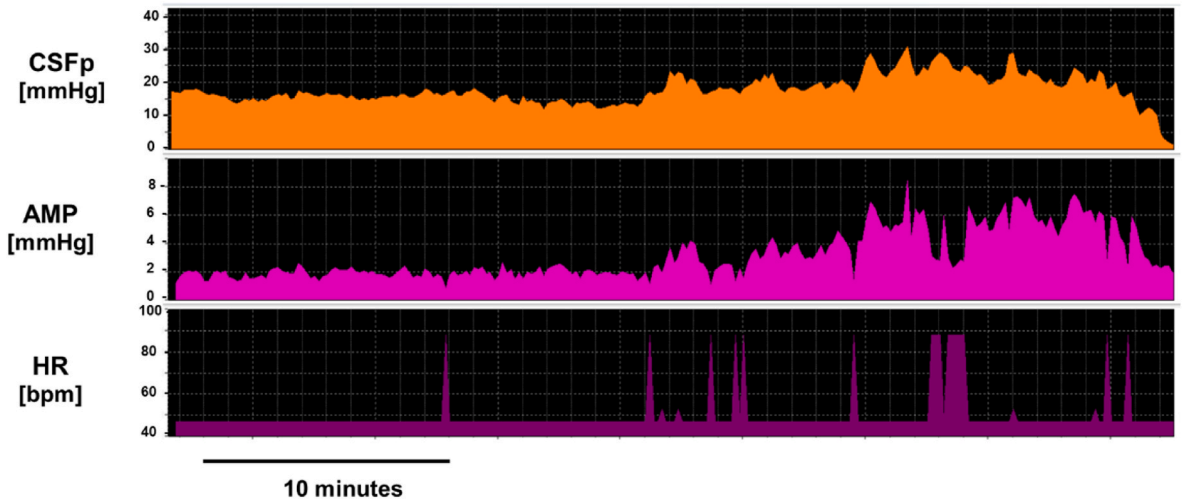


Fig. 5. Cerebrospinal Fluid Infusion test in patient with Idiopathic Intracranial Hypertension (PTCS, no cause identified). The patient had high grade papilloedema with recorded "normal" CSFp of 13–15 mmHg.

observed patients with high variability in ICP, both during the day, as well as overnight (Fig. 2). ICP appeared normal or borderline (18–20 mmHg), with high amplitude, vasogenic waves as high as 60–70 mmHg.

The majority of the recordings demonstrated a "normal" to borderline raised CSF pressure (Figs. 3–5). Of those, few patients with diagnosed IIH had "normal" CSFp at baseline with significant raise of CSFp during infusion (**3**). Those patients tended to present with less clear clinical symptoms and mild to moderate papilloedema.

There was a group of patients that presented very similar to those with raised ICP and high grade papilloedema, with recorded CSFp in ranges as low as 10 mmHg and only showing disturbance of CSF dynamics during infusion, with significant increase in CSFp from baseline (Fig. 4).

Finally, in this group, some patients with classical symptoms and papilloedema showed "normal" CSF opening pressure, without significant increase during infusion (Fig. 5).

Group B: ICP/CSF pressure recordings with knowledge of the venous sinus pressure.

In one patient, fluctuations in ICP from 0 to 60 mmHg were observed in response to the opening and collapse of the internal jugular veins and transverse venous sinuses (Fig. 6).

In relationship to the Sagittal sinus pressure (SSp) and in patients with described, pathological coupling between their CSFp & SSp (total of 10 cases previously studied), some exhibited normal to borderline raised CSFp (Fig. 7).

The increase in CSFp during infusion was variable and included either small increments of 4–8 mmHg (Fig. 8), or significant increments of >12 mmHg (Fig. 9).

4. Discussion

We have identified significant variability in the CSF pressure amongst different patients with PTCS. Over the years, we have also been able to observe the interactions between CSF and Venous Sinus Pressures.

Venous sinus stenting has offered pioneering and less invasive treatment than shunting to PTCS patients, and tenting versus shunting remains one of the priorities in the management of PTCS patients. However, our understanding of the condition remains limited, whilst elucidating the disease mechanisms remains crucial. CSF dynamics can offer investigations directly into the heart of the mechanisms of PTCS and are useful both for physiological research, as well as for aiding the management of complex patients.

Interestingly, the combination of the observed patterns and parameters in our patients, including CSFp baseline, SSp, rise in CSFp during infusion and presence of coupling between SSp could provide more information about the heterogeneity of PTCS: when studied, those parameters would yield 16 separate different pathophysiological patterns. All combinations appear possible, except potentially for normal SSp in the presence of CSFp-SSp coupling. Further recordings are required to elucidate this.

4.1. CSF/intracranial pressure must be confirmed as elevated

High CSFp is frequently observed in PTCS and can range from 20 to 40 mm Hg in most cases. However, ICP or CSFp in PTCS can be elevated in different ways. We have previously stressed the importance of using a reliable method for measuring and monitoring CSFp, especially due to the reliance of current perception and criteria of PTCS/IIH on a pressure threshold (Lalou et al., 2020a; Friedman and Liu, 2013; Smielewski et al., 2008). Both overnight ICP monitoring, and CSF infusion test, offer a steady, longer-term recording and not a snapshot measurement of pressure over a few seconds.

In patients with such heterogeneity in ICP, our results corroborate the rationale behind ensuring gold standard measurement of pressures, preferably in a specialised setting (Lewis et al., 2012; Balestreri et al., 2004; Kasprowicz et al., 2016; Czosnyka et al., 1988). Highlighting the importance of not relying on CSFp as a number or even diagnostic "threshold", are the cases where patients had classic signs and symptoms of PTCS with high-grade papilloedema, and their infusion tests showed "normal" CSP baseline, with or without significant rise during infusion (Group A, patterns 3&4).

In our study, we have frequently found what could be considered as a "classic" pattern expected for PTCS, with stable, raised ICP, and no significant rise in the pressure during infusion. As demonstrated, it is not the only pattern observed.

4.2. Assessing CSF dynamics in IIH

As we have shown from our recordings, ICP could segmentally appear misleadingly "normal" (even <15 mmHg).

The pattern observed of CSFp baseline <18–20 mmHg (even <15 mmHg at times), with strong b-waves and elevated Rout during infusion, is normally seen in Normal Pressure Hydrocephalus (Czosnyka, 2013; Czosnyka et al., 2004, 2007b). The identification of such patterns in PTCS raises many questions regarding the mechanisms, as well as the clinical diagnosis of these patients (with a CSFp <18 mmHg, they would not meet the diagnostic criteria).

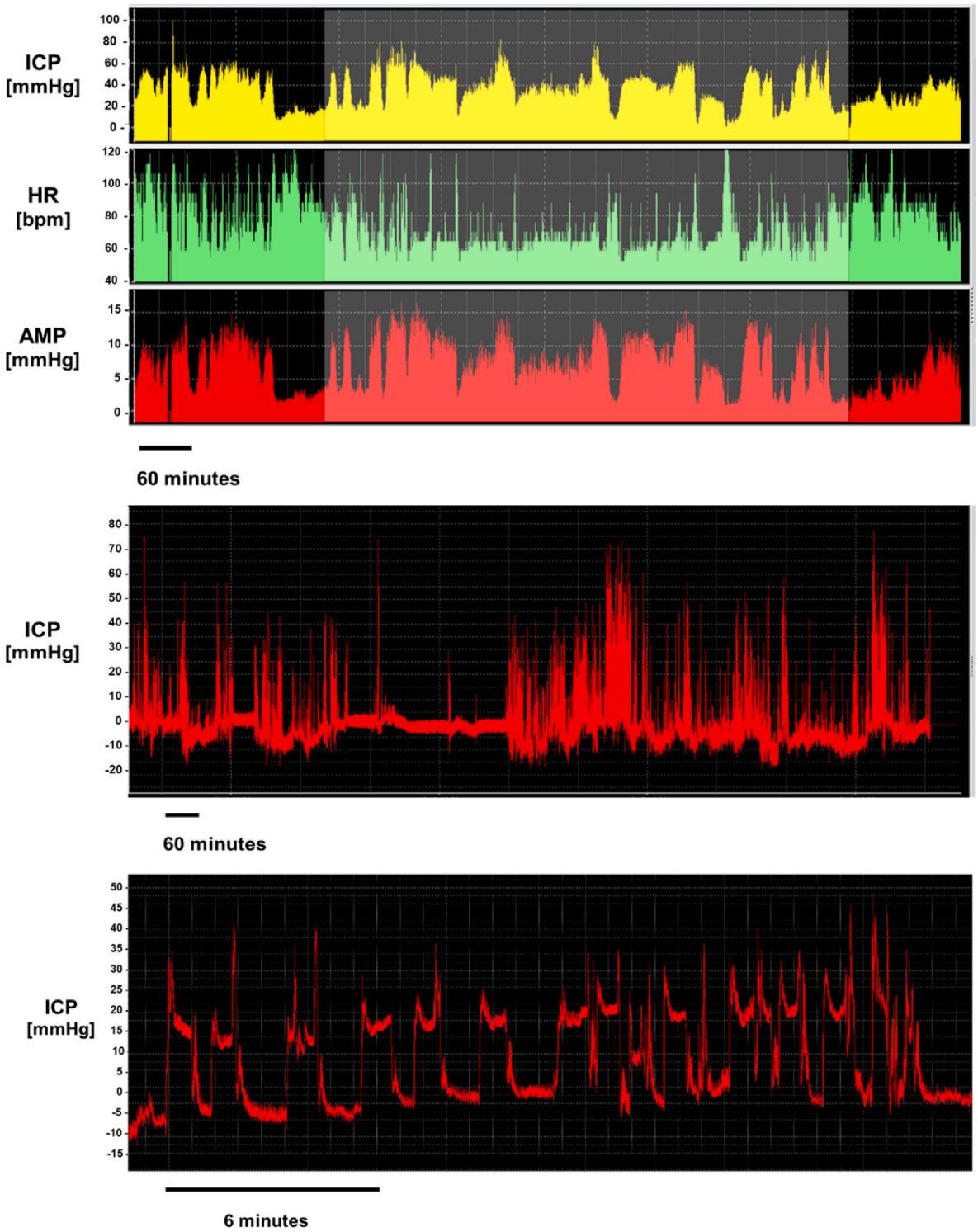


Fig. 6. Overnight ICP monitoring of unstable pressure fluctuations in PTCS patient due to opening and collapse of transverse venous sinus. Upper panel: overnight recording of ICP ranging from 0 to 60 mmHg. Middle panel: Raw data from the ICP recording, demonstrating the high instability and wide range of ICP fluctuations. Lower panel: Closer look into the ICP waveform from the raw data showing extreme ICP waveform amplitude, most likely corresponding to venous pulsations. Switching between collapsed and open transverse sinus may have adynamic character and produce deep fluctuations of ICP.

It is particularly challenging to understand the behaviour of Rout in PTCS, as it appears different patients within the same syndrome have vast differences in anatomy, pathophysiology and CSF circulation. It would be important to investigate whether a "normal" Rout could be due to LP induced CSF leak or even the co-existence of CSF leak in those patients (Czosnyka et al., 2005; Eisenträger et al., 2013; Lalou et al., 2020c). Whilst challenging, CSF leak is a quintessential component of the PTCS spectrum and relevant investigations should be developed and integrated into our studies of those patients.

Methodologically, it would be erroneous to expect any of the disturbances in those components to be reflected in a singular, isolated, ICP measurement. First and foremost, we know physiologically that there is a close interaction between CBF and ICP, not only mediated through changes in cerebral perfusion pressure (CPP). As such, disturbances in

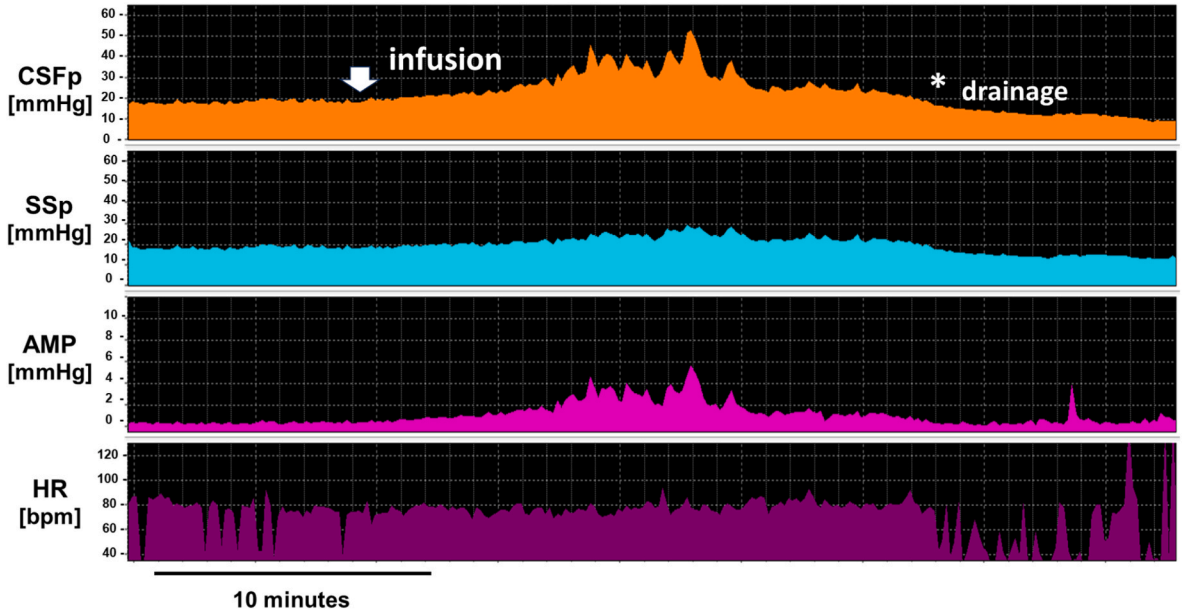


Fig. 7. Coupled CSFp and SSp in PTCS patient with "borderline" baseline pressure. CSFp and SSP are coupled both at baseline and at plateau. "Borderline normal" CSFp baseline (18 mmHg), significant increment in pressure during infusion with slow waves of >40 mmHg.

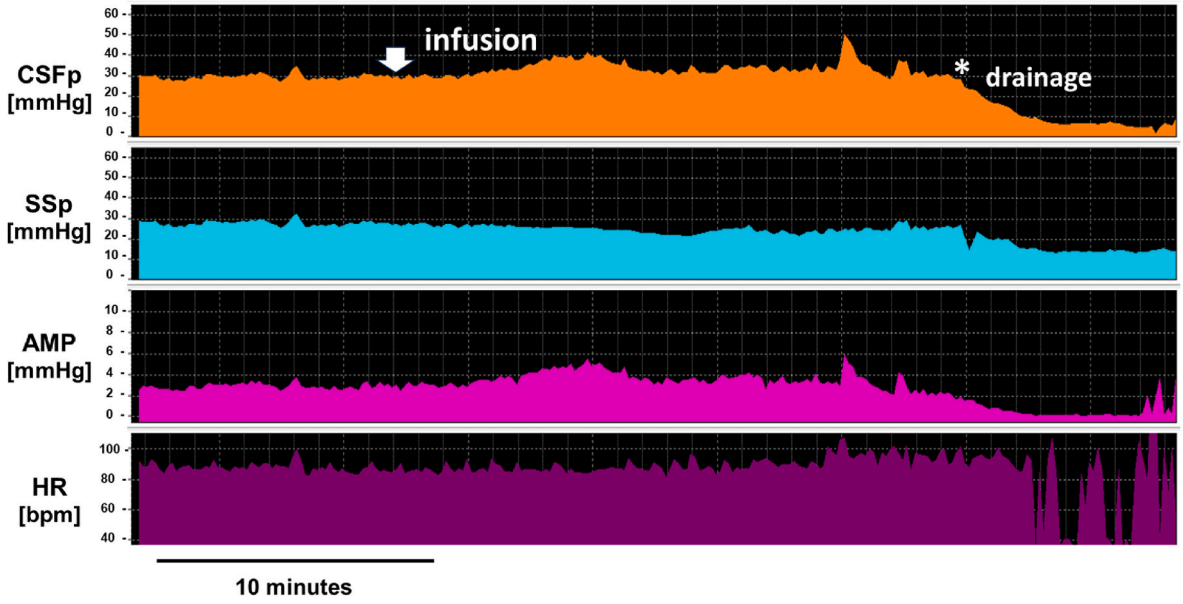


Fig. 8. Coupled CSFp and SSp in PTCS patient with mild increase in CSFp during infusion. CSFp and SSP are coupled both at baseline and at plateau. Raised CSFp baseline (30 mmHg), with mild increment in pressure during infusion (34 mmHg).

ICP will arise not only from issues in CSF formation, circulation, and absorption, but there is also an important vascular component (Czosnyka et al., 2007b, 2008, 2009; Weerakkody et al., 2012; Schmidt et al., 2008; Bateman, 2000; Jaraj et al., 2016; Wilson, 2016; Piechnik et al., 2008). Vasogenic waves can produce significant oscillations in pressure that, if not recorded and analysed appropriately, can lead to misunderstandings on the behaviour of ICP in some patients. Figs. 2 and 4 show two rare examples of IIH patients with significant activity of vasogenic waves causing changes from low to very high levels of ICP as steady states.

For PTCS patients, any method for monitoring ICP (Transcranial Doppler, ICP telemetry, etc) would be more complete and comprehensive if it follows the same dynamics principles of analysing continuous waveforms and exploring influencing factors of ICP (Budohoski et al., 2012; Cardim et al., 2016a, 2016b; Kirkpatrick et al., 1996; Schmidt et al., 2002, 2008). Methods that rely on measurement of ICP at a single time point, such as optic nerve sheath diameter, lumbar puncture, spontaneous venous retinal pulsations, need to be used with vigilant awareness of their limitations against any practical use in case of clinical resources or urgency.

4.3. *Cerebral venous sinus pressures in PTCS*

Cerebral venous pressure, particularly SSp, displays interesting characteristics and variability in PTCS. It can be coupled not only in static, mean values but also in their dynamic contents of the two pressures, mainly the pulse amplitude and the slow waves (Pickard et al., 2008; Lalou et al.). Thus, we can confirm the role of venous sinus

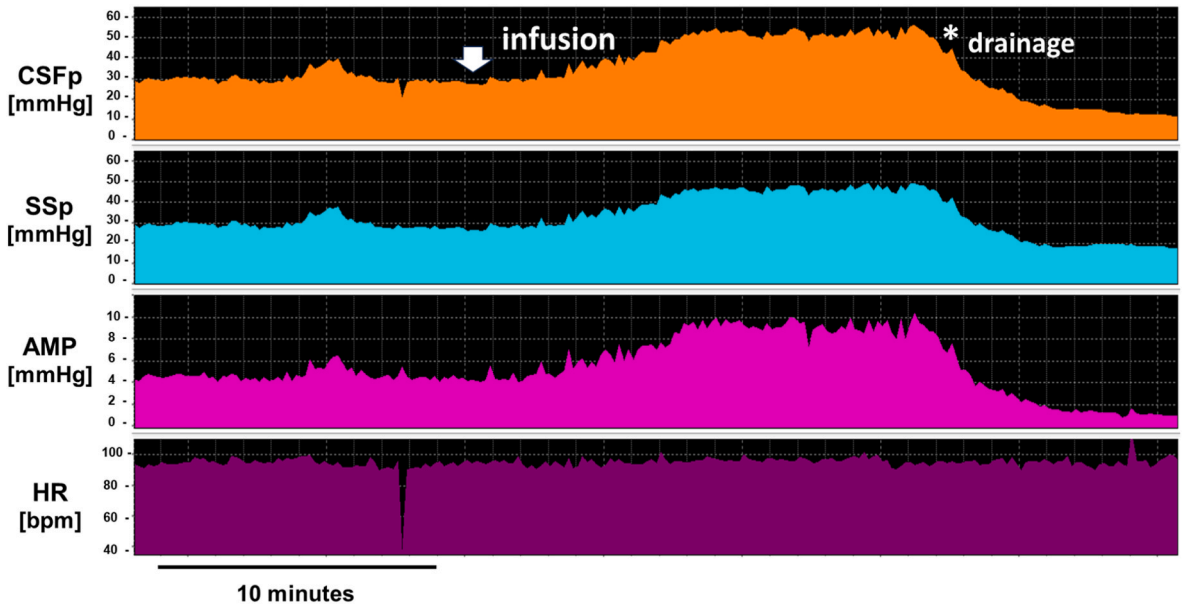


Fig. 9. Coupled CSFp and SSp in PTCS patient with raised baseline pressure and significant raise of CSFp during infusion. CSFp and SSP are coupled both at baseline and at plateau. Raised CSF baseline (30 mmHg), significant increment in pressure during infusion (54 mmHg). As a rare exception, the infusion was allowed to continue after CSFp >40 mmHg under the care of consulting physicians and with controlled monitoring, for a limited time only (7 min).

collapsing in generating significantly raised CSFp, or at least contributing to the pathophysiology of PTCS via a circular coupling between CSFp and SSp.

However, in PTCS, SSp and CSFp exhibit remarkable parallel variability and are more than a single number. The cerebral venous sinuses are a very heterogeneous system that remains difficult to study anatomically and physiologically (Chang et al., 2003; Martins et al., 2009; Kristensen et al., 1992; Owler et al., 2003; Johnston, 1973; Janny et al., 1981). Under dynamic conditions (infusion tests, overnight sleep etc), this heterogeneity increases even further. An example of such variability is secondary thrombosis and narrowing of the cerebral venous sinuses, that in turn are recognised causes of PTCS, have been shown to increase SSp without any changes during infusion. We have observed this in a traumatic brain injury patient with fixed transverse sinus stenosis (unpublished data).

The patterns observed for the patients in whom SSp was monitored (Group B), may have various explanations around the observed differences in CSFp baseline, during infusion (and subsequently Rout), and the interactions between CSFp and SSp:

In cases where there is no fixed stenosis, but a state of compressible venous sinuses, any rise in CSFp can decrease its lumen, which increases the hydrodynamic resistance for sinus blood flow, increasing in the same way the SSp (if cerebral blood flow stays constant), which in turns increases CSFp.

In cases of fixed stenosis, a superadded resistor in the system possibly creates two different CSFp-SSp gradients, and subsequently two different resistors. In the cases we have described, whereby there is a collinearity between CSFp and SSp and a small pressure gradient, Rout is calculated as normal, even lower than normal controls. Individual studies are required to differentiate these separate scenarios (Eklund et al., 2007; Pickard et al., 2008; Lalou et al.).

Based on our observations, we cannot ascertain the behaviour of the CSFp-SSp interaction in all PTCS cases. As illustrated from the cases where interactions were quintessential, there is a potential need to study both pressures, rather than each pressure in isolation that provide no research or clinical insights.

Which mechanism is responsible for elevated CSFp in PTCS?

Assuming that SSp is generally elevated in PTCS in most patients, due to well described fixed venous stenoses or CSFp-SSp coupling we can understand that increased CSF formation rate plays a minimal role in increasing the CSF pressure (Martins et al., 2009; Kristensen et al., 1992; Karahalios et al., 1996). Similarly, other influencing factors, such as obesity, would play a minimal role in driving CSFp upwards, other than adding to an already disturbed system via some increase of the abdominal pressure and/or the central venous pressure. Thereafter, reduction of the CSF production rate as a therapeutic target would also have minimal effect on CSFp (reduction of 0.75 mmHg if CSF formation rate halved, 1.5 mmHg maximum if reduced to 0).

4.4. *Papilloedema & implications in management of PTCS*

After our exploration of the observed cases in our centre, we have noticed a plethora of interactions between different elements of PTCS.

An important point for both future research as well as clinical consideration, would be the relationship between CSFp, SSp and the presence or absence of papilloedema. We have reported a tendency for both the presence as well as the degree of the papilloedema to not correlate with the CSFp and CSF dynamics. In cases with completely normal CSFp (as measured by longer-term monitoring) and normal dynamics, it is possible that the term optic disc oedema, rather than papilloedema, should be applied and alternative diagnoses to PTCS should be considered (Lalou et al., 2020a; Andrews et al., 2014; Matthews et al., 2017; Martins et al., 2009; Bateman, 2008). However, the clinical presentation also indicating PTCS should of course not be dismissed. Accurate diagnosis and treatment should follow an accurate understanding of the combined anatomy, physiology and clinical spectrum of the syndrome.

Prospective studies focusing on discovering and mapping out different potential mechanisms of the syndrome need to be carried out. Mechanistic understanding of the condition could be the key to leading successful randomised controlled trials. As such, aiming to treat will be superseded by investigating the mechanisms of SSp and CSFp, interrupting the reported pathophysiological findings and maximising potential effects of stenting versus shunting, generalising them to the right subpopulations within the complex entity that is PTCS.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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