Research

Lumbar puncture, chronic fatigue syndrome and idiopathic intracranial hypertension: a cross-sectional study

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Summary

Objective: Unsuspected idiopathic intracranial hypertension (IIH) is found in a significant minority of patients attending clinics with named headache syndromes, if it is specifically sought out. Chronic fatigue syndrome is frequently associated with headache. Could the same be true of chronic fatigue? Moreover, there are striking similarities between the two conditions. Could they be related? Attempting to answer these questions, we describe the results of a change in clinical practice aimed at capturing patients with chronic fatigue who might have IIH.

Design: Cross-sectional.

Setting: Hospital outpatient and radiology departments.

Participants: Patients attending a specialist clinic with chronic fatigue syndrome and headache who had lumbar puncture to exclude raised intracranial pressure.

Main outcome measures: Intracranial pressure measured at lumbar puncture and the effect on headache of cerebrospinal fluid drainage.

Results: Mean cerebrospinal fluid pressure was 19 cm H₂O (range 12–41 cm H₂O). Four patients fulfilled the criteria for IIH. Thirteen others did not have pressures high enough to diagnose IIH but still reported an improvement in headache after drainage of cerebrospinal fluid. Some patients also volunteered an improvement in other symptoms, including fatigue. No patient had any clinical signs of raised intracranial pressure.

Conclusions: An unknown, but possibly substantial, minority of patients with chronic fatigue syndrome may actually have IIH. An unknown, but much larger, proportion of patients with chronic fatigue syndrome do not have IIH by current criteria but respond to lumbar puncture in the same way as patients who do. This suggests that the two conditions may be related.

Keywords
chronic fatigue syndrome, idiopathic intracranial hypertension, headache, lumbar puncture

Introduction

There are similarities between chronic fatigue syndrome and idiopathic intracranial hypertension (IIH), the first characterized by fatigue, the second by headache, both conditions of unknown aetiology which can develop, without any clear precipitating event in either sex, at almost any age and giving symptoms that can last for years.¹⁻⁷ Fatigue, a requisite in chronic fatigue syndrome, is common in IIH. Headache, usual in IIH, is common in chronic fatigue. Impaired memory and concentration, dizziness, joint pains and depression occur in both.¹⁻³⁻⁷⁻¹¹

Chronic fatigue syndrome is defined by symptoms alone and presents no clinical signs. IIH is defined by the presence of raised intracranial pressure but presents no clinical signs other than those of raised intracranial pressure itself, signs which may be absent.¹²⁻¹³

Typically, IIH is seen in young obese women and usually there is headache and visual disturbance, with papilloedema the hallmark of raised intracranial pressure. Headache may be absent, however, in which case the diagnosis is usually made after papilloedema is discovered by an optician or during fundoscopic examination for visual symptoms.¹⁴ Sometimes papilloedema is absent and the cause of headache is only established after a high cerebrospinal fluid (CSF) opening pressure is found at lumbar puncture.¹⁵⁻¹⁷

These atypical cases are generally perceived to be rare and can require some commitment on the part of the physician to diagnose. Nonetheless, if they do exist, then so also must cases with neither headache nor papilloedema. Of what symptoms would these patients complain? Likely, it would be of the other symptoms found in IIH – fatigue, memory and
concentration problems, 7-11 that is, the sort of symptoms that form the foundation of a diagnosis of chronic fatigue syndrome.1,3

At the same time, it is has been established that IIH without any signs of raised intracranial pressure will be found in a significant minority of patients attending clinics with named headache syndromes, if it is specifically sought out.15-17 So, is IIH especially being missed if there is also complaint of headache? To confront this possibility, we have extended the diagnostic work-up of patients with chronic fatigue to specifically exclude raised intracranial pressure when headache is a prominent symptom.

Patients and methods

From 2007 patients attending a specialist clinic with chronic fatigue, who satisfied the accepted criteria for chronic fatigue syndrome,1 in whom headache was a significant complaint, and in whom CT presented no contraindication, have been offered lumbar puncture to measure CSF pressure. The CSF pressure measurements, themselves, have been the subject of a previous paper.18 This paper describes also the clinical effects of CSF drainage, undertaken at the same time, in the same group of patients.

Lumbar puncture was carried out with the patient lying on their left side using a 22 gauge needle attached to a manometer with pressures referenced to zero at the point of needle insertion. CSF drainage was by gravity under medical supervision. The amount to be drained was not specified beforehand. CSF drainage was discontinued if there was onset of a new headache.

Results

Twenty patients in total had lumbar puncture, seven males and 13 females with an average age of 35 years (range 16–60 years) and average body mass index of 27 kg/m². All satisfied the accepted criteria for chronic fatigue syndrome1 All had had symptoms for at least six months, the longest for 30 years. No patient had papilloedema or any other sign of raised intracranial pressure.

Five patients had CSF pressures of greater than 20 cm H₂O, four of whom fulfilled the second edition international classification of headache disorders (ICHD-2) criteria for IIH.19 These latter four patients were relabelled as IIH and treated accordingly. Mean CSF pressure was 19 cm H₂O (Table 1).

CSF withdrawal produced a symptomatic improvement in 17 patients, that is in all five patients whose CSF pressures were greater than 20 cm H₂O and in 12 patients whose pressures were between 12 and 20 cm H₂O. This improvement usually developed during, or soon after the procedure and lasted from a few minutes to several weeks. It generally took the form of reduced headache, a heightened alertness and a reduced sense of fatigue (Table 2).

Eleven patients developed low pressure headaches. These usually became apparent the day after lumbar puncture and in some cases were severe, lasting up to two weeks. Some patients who had shown early improvement before the onset of low pressure symptoms recovered the benefit for a time once low pressure symptoms had resolved.

Discussion

This study suggests that if headache is a prominent symptom in patients diagnosed with chronic fatigue syndrome, then a substantial minority will have raised intracranial pressure and will respond with symptomatic improvement to a reduction in intracranial pressure by CSF withdrawal. These patients would then fulfil the diagnostic criteria for idiopathic IIH and should be diagnosed as such. This study also suggests that in the same group of patients with headache and chronic fatigue, there will be a much larger proportion who will respond to a reduction in intracranial pressure in exactly the same way as patients with IIH but whose intracranial pressure is not high enough to allow a formal diagnosis of IIH by currently accepted diagnostic criteria.

Clearly, we are looking at a highly selected group of patients. This is a product of the particular approach used in this work, in which the clinician was effectively given licence to choose for further investigation those patients in whom he thought it was not unreasonable to look for raised intracranial pressure. We used this approach because it was the most efficient way of finding out whether our suspicion that IIH was being missed in patients with chronic fatigue was misguided or whether it had some legitimacy. The results seem to lend support to the idea, at least with regards to local practice, but in no way do they establish the prevalence of IIH in patients with chronic fatigue.

At the same time, we made no attempt to prescribe the type of headache that might precipitate a lumbar puncture and we have not looked at the headache phenotype in patients who were referred. This is because we were unconvinced that stratifying patients according to their headache phenotype would be particularly helpful to the aims of this work; in the event, a supposition born out by our results. The only stipulation was that headache should be a prominent
symptom with the rest left entirely to the discretion of the physician (AL) running the clinic. This does mean, however, that we can give no indication of the type of headache that might suggest raised intracranial pressure in these patients and little indication of its severity. So, there can be no firm guidance to other clinicians of when raised intracranial pressure should be sought out or when it should not, although we can say that the possibility should not be ignored.

Of course, relying on a clinician’s acumen to select patients for lumbar puncture invites the criticism that his acumen may have been poor before it was raised to acceptable standards by the introduction of a new working practice. We counter this by saying that all patients were seen in a specialist clinic as before. They all satisfied the accepted criteria for chronic fatigue syndrome and none had any clinical evidence of raised intracranial pressure. At the same time, it would be difficult to envisage improved clinical acumen accounting for the results of CSF drainage in those patients whose intracranial pressure was within normal limits. These patients would not be expected to have any signs of raised intracranial pressure. Their headache would not be expected to reflect abnormal intracranial pressure and, at our current level of understanding, they would not be expected to offer any clues to the clinician that might suggest a favourable response to lumbar puncture.

Table 1. Characteristics of 20 patients diagnosed with chronic fatigue syndrome who had lumbar puncture.

| CSF pressure (cm H₂O) | BMI (kg/m²) | Sex | Age | Length of history (years) |
|-----------------------|-------------|-----|-----|--------------------------|
| 41*                   | 36          | F   | 40  | 1.5                      |
| 29*                   | 31          | M   | 53  | 6                        |
| 25*                   | 27          | M   | 60  | 10                       |
| 22*                   | 22          | M   | 21  | 3                        |
| 21                    | 39          | F   | 46  | 2.5                      |
| 20                    | 27          | F   | 22  | 5                        |
| 20                    | 30          | M   | 39  | 5                        |
| 20                    | 36          | F   | 49  | 11                       |
| 19                    | 31          | F   | 26  | 13                       |
| 19                    | 23          | F   | 16  | 0.5                      |
| 17                    | 18          | F   | 20  | 0.8                      |
| 17                    | 30          | F   | 22  | 8                        |
| 17                    | 31          | M   | 18  | 0.8                      |
| 15                    | 23          | M   | 62  | 15                       |
| 15                    | 26          | M   | 47  | 0.5                      |
| 14                    | 20          | F   | 23  | 12                       |
| 14                    | 21          | F   | 27  | 9                        |
| 12                    | 23          | F   | 47  | 30                       |
| 12                    | 27          | F   | 22  | 3                        |
| 12                    | 22          | F   | 41  | 12                       |

BMI: body mass index (normal, 18.5–25; overweight, 25–30; obese >30).
*Match ICHD-2 criteria for IIH.
More problematic in the interpretation of our results is that all lumbar punctures were performed and all pressure measurements were recorded by a single observer (NH) who had a strong interest in the results. This reflects the circumstances in which the lumbar punctures were undertaken – that is in the course of investigating these patients as part of their ongoing clinical management, with clinical decisions dependent on the outcomes, no different to other patients being investigated in the same way. Bias, however, cannot be excluded, though it would have to be very strong indeed to account for all our findings.

Similar concerns apply to recording the effects of CSF drainage on symptoms. Many patients were able to attest to the effect of lumbar puncture in the clinic afterwards, but in some the benefit was brief and harder to remember later, once they had relapsed to their previous condition. It would take a more formal academic approach to resolve this issue but, again,
bias would have to be very strong indeed here to wipe out our results.

Reassuring in this regard, however, is to make comparison with earlier studies. These have shown that if IIH is specifically sought out in patients with headache, even if they have a defined headache syndrome and no evidence of raised intracranial pressure it will still be found in up to 14% of cases.\textsuperscript{15–17} So, in some sense, it is not particularly surprising that in our patient group, selected on the basis of headache, we found cases of IIH.

What is noteworthy, however, is to have achieved a pick up rate of 20% in a group of patients who in their clinical syndrome presented no more than an unspecified degree of prominence of a common symptom (headache). These patients would not normally attract lumbar puncture. Indeed, lumbar puncture might be considered over investigation of patients with a settled diagnosis of chronic fatigue syndrome. Lumbar puncture was performed because the clinician was primed by the knowledge that chronic fatigue syndrome and IIH have many features in common and that, regardless of its phenotype, raised intracranial pressure as a cause of headache is not infrequent and can only be excluded by measuring it.

Equally noteworthy is the response of these patients to CSF drainage, a key criterion by which headache is judged to be caused by raised intracranial pressure. Seventeen patients described an improvement in headache with CSF drainage, many of whom had CSF pressures in the normal range. This finding raises intriguing questions about the relationship between the symptoms of chronic fatigue syndrome and intracranial pressure and invites speculation that there might be a connection between chronic fatigue syndrome and IIH.

In 2002, Friedman and Jacobson\textsuperscript{6} re-examined the diagnostic criteria for IIH, effectively defining IIH as proven if CSF pressure was greater than 25 cm H\textsubscript{2}O and there was no identifiable cause. Symptoms and signs were not mandatory but, if they were present, could only reflect raised intracranial pressure.

Some patients who are strongly suspected of having IIH, however, may have CSF pressures within the normal range on initial testing. In these cases, repeat lumbar punctures may catch fluctuations in intracranial pressure above the upper limit of normal. In others, a prolonged period of CSF pressure monitoring might be necessary to confirm the diagnosis.\textsuperscript{11,20} In others again, the diagnosis will remain unconfirmed and treatment of headache will be symptomatic.

In 2004, the International Headache Society formulated a set of criteria by which a headache could be attributed to IIH.\textsuperscript{19} Amongst these, intracranial pressure had to be greater than 20 cm H\textsubscript{2}O (or 25 cm H\textsubscript{2}O in obese individuals) but of key importance was that headache had to respond to a reduction in intracranial pressure produced by CSF withdrawal at lumbar puncture. If headache did not respond, the implication was that raised intracranial pressure was unlikely to be the cause, even if it were present.

Not addressed in this document, however, is what it would mean if a patient had CSF pressures insufficient to diagnose IIH but whose headache still responded to CSF withdrawal; a problem posed by our particular observations. Thus, in our group of patients, five had CSF pressures of more than 20 cm H\textsubscript{2}O, all of whom responded to CSF drainage. Do all of these patients have IIH or only the four whose weight and CSF pressure combinations also satisfy the other ICHD-2 criteria? Fifteen patients in our series had CSF pressures between 12 and 20 cm H\textsubscript{2}O, 12 of whom responded to CSF drainage. Do all of these 12 responders also have IIH or do none of them because they fail to reach the other ICHD-2 criteria? This is a conundrum not considered previously and suggests two possible answers: either the CSF withdrawal test is very strongly tainted by a placebo effect or disorders of IIH begin at much lower levels of intracranial pressure than currently recognized.

With respect to the first, it is impossible to estimate the placebo effect of CSF withdrawal without a control group. Nevertheless, the response rate to CSF withdrawal in our patients would be far beyond what would normally be attributed to placebo in clinical practice or research.\textsuperscript{21,22} Moreover, CSF withdrawal is a procedure in common use in IIH whose mechanism is broadly understood, the principles of which form the basis of treatment.\textsuperscript{11,23} It would be difficult to discredit the results of the test in our patient group without calling into question its value in patients with unequivocal IIH.

The second, therefore, is the more likely; that is, that disorders of raised intracranial pressure begin at much lower pressures than currently recognized. In this regard, it is worth noting that the CSF pressures that define the normal range are not based on an empirical knowledge of what is normal and what abnormal but is simply a product of statistical probability.\textsuperscript{23–25} It is axiomatic, therefore, that there will be patients who have a condition of abnormal intracranial pressure identical to IIH in terms of its pathogenesis and clinical features but whose CSF pressures lie within the normal range. In this situation, one would expect the clinical response to CSF drainage to be telling.

Of further concern is the provenance of normative values for CSF pressure in the first place. Recently
these have come, not from asymptomatic normal volunteers, but from patients whose symptoms are thought not to derive from abnormal intracranial pressure. This must be a difficult one to judge: some patients with proven raised intracranial pressure offer almost no clinical evidence for it bar headache, and some not even that. Yet, this has not prevented papers purporting to define normal reference values for CSF pressure from including patients with headache in their study groups. In fact, to the contrary, patients with headache or with unexplained symptoms often comprise a sizable proportion of the subjects in these studies.24,25 How can one be sure that these patients do not have an unrecognized disorder of high intracranial pressure?

Fatigue is a defining feature of chronic fatigue syndrome but headache is common. Our patients were selected for lumbar puncture because headache was prominent and there was legitimate clinical concern that a diagnosis of IIH was being overlooked. This could mean that our results may not have any bearing on the wider group of patients with chronic fatigue where severe headache is not a particular feature. Nevertheless, with 20% of the group positive for IIH by the ICHD-2 criteria and 85% responding to CSF withdrawal, it would be remarkable if they did not. By the same token, it would be also be remarkable if the results could all be accounted for by observer bias.

Is it possible, then, that chronic fatigue syndrome represents an incomplete form of IIH, with average CSF pressures much lower than in the syndrome in full, usually manifesting subtler symptoms, but characterized by a favourable symptomatic response to lumbar puncture? Equally, is it possible that the currently accepted normative data on CSF pressures are excluding patients from being diagnosed with a disorder of high intracranial pressure when, in fact, this is what they have? Our results suggest that these are areas that would benefit from further study.

**Declarations**

**Competing interests:** None declared

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**Guarantor:** NH

**Contributorship:** NH conceived the study, researched the literature and collected the data. NH had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed substantially to data analysis, data interpretation and writing.

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