



Chronic fatigue syndrome and idiopathic intracranial hypertension: Different manifestations of the same disorder of intracranial pressure?



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ABSTRACT

Though not discussed in the medical literature or considered in clinical practice, there are similarities between chronic fatigue syndrome and idiopathic intracranial hypertension (IIH) which ought to encourage exploration of a link between them. The cardinal symptoms of each – fatigue and headache – are common in the other and their multiple other symptoms are frequently seen in both. The single discriminating factor is raised intracranial pressure, evidenced in IIH usually by the sign of papilloedema, regarded as responsible for the visual symptoms which can lead to blindness. Some patients with IIH, however, do not have papilloedema and these patients may be clinically indistinguishable from patients with chronic fatigue syndrome. Yet IIH is rare, IIH without papilloedema (IIHWOP) seems rarer still, while chronic fatigue syndrome is common. So are the clinical parallels spurious or is there a way to reconcile these conflicting observations?

We suggest that it is a quirk of clinical measurement that has created this discrepancy. Specifically, that the criteria put in place to define IIH have led to a failure to appreciate the existence, clinical significance or numerical importance of patients with lower level disturbances of intracranial pressure. We argue that this has led to a grossly implausible distortion of the epidemiology of IIH such that the milder form of the illness (IIHWOP) is seen as less common than the more severe and that this would be resolved by recognising a connection with chronic fatigue syndrome.

We hypothesise, therefore, that IIH, IIHWOP, lesser forms of IIH and an undetermined proportion of chronic fatigue cases are all manifestations of the same disorder of intracranial pressure across a spectrum of disease severity, in which this subset of chronic fatigue syndrome would represent the most common and least severe and IIH the least common and most extreme.

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Introduction

Though not discussed in the medical literature, there are similarities between chronic fatigue syndrome and idiopathic intracranial hypertension (IIH) which ought to encourage exploration of a link between them. Thus, headache which is the cardinal symptom of IIH is frequent in chronic fatigue [1,2]. Fatigue, though often eclipsed by headache, is a common feature of IIH [3]. Other symptoms – poor memory, inability to concentrate, low mood, dizziness, muscle and joint pains – are seen frequently in both [1–6]. Patients with IIH often conform to a particular phenotype – young, obese, female – but either condition can develop at almost any age, in

either sex, giving symptoms that can last for years. Both conditions are diagnoses of exclusion; in the case of IIH this means of known causes of raised intracranial pressure; in the case of chronic fatigue this means of any other illness, including IIH, that might be a cause of fatigue. Both are of unknown aetiology [1–5,7].

The key discriminating factor between these two conditions is the presence of raised intracranial pressure. Patients with chronic fatigue syndrome (who by definition must have normal intracranial pressure) display no physical signs. Patients with IIH (who by definition must have raised intracranial pressure) display only signs of raised intracranial pressure, usually papilloedema. These signs may be absent, however [8–10], in which circumstances the two conditions become clinically indistinguishable. This raises the probability that some patients with chronic fatigue will have unrecognised intracranial hypertension [11] and the possibility that the two conditions might be connected [12].

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The epidemiology of these syndromes, on the other hand, seems to belie this notion, IIH recognised as rare and overwhelmingly a disease of women [3–7]; chronic fatigue syndrome a condition affecting both sexes more equally (although with a female preponderance) and at least two orders of magnitude more common [1,2,13,14]. So, are the clinical parallels spurious or is there a way to reconcile these conflicting paradigms?

Idiopathic intracranial hypertension

Idiopathic intracranial hypertension (IIH) is a rare but well described condition of raised intracranial pressure of unknown cause characterised by headache and visual symptoms [3–7]. Patients with IIH display no physical signs, except those of raised intracranial pressure – mainly papilloedema. The typical case is not a difficult diagnosis though variant forms do occur. 10% of patients, for example, do not complain of headache [7]. 5% do not have papilloedema (IIHWOP), this latter group usually diagnosed when headache symptoms are severe enough to prompt a lumbar puncture [8–10]. Inevitably, if these variants exist, there must also be patients with IIH who have neither papilloedema nor headache, though they might be an order of magnitude less common again.

IIH and IIHWOP are diagnosed by the same criterion of intracranial pressure whereby the cerebrospinal fluid (CSF) opening pressure should be greater than 25 cm H₂O [15]. Nevertheless, IIHWOP seems to be a less severe form of the condition generally showing lower pressures than IIH in full and being much less likely to result in visual loss [9]. IIH with neither papilloedema nor headache would predictably be a milder form still. This presents a conundrum, however, because it suggests that the most virulent form of the illness is the most common, a circumstance which would require a reversal of the usual relationship between relative frequency and disease severity in chronic conditions. Is this credible and what might be the explanation? Are milder cases, for example, being under reported?

There is no doubt that looking for IIH, in the absence of papilloedema, is not particularly rewarding. In the first place IIHWOP is understood to be rare. Secondly, there are no clues in the headache phenotype or clinical examination that would exclude it [16–18]. Third, there is little danger of catastrophic complications if the diagnosis is missed and, finally, treatment options appear to be limited even if there is a diagnosis to be made [9,10,15]. This means there is little anxiety on the part of the clinician over a missed diagnosis, circumstances which can only reinforce the prevailing view on its infrequency.

Restoration of the usual relationship between relative frequency and disease severity, however, would require that the prevalences of IIH without headache, IIHWOP, and by extension IIH with neither papilloedema nor headache, are being underestimated on a very large scale indeed. Is this possible? Yes, but only if these conditions were truly asymptomatic or gave rise to symptoms and diagnoses in which the possibility of an underlying abnormality of intracranial pressure would almost never be considered. Of what symptoms might these patients complain, therefore, and what diagnoses might they be given as a result? By inference they would complain of the other symptoms that accompany IIH: fatigue, poor memory, inability to concentrate, low mood, dizziness, muscle and joint pains, with or without headache [4–7]. In effect, symptoms that form the foundation of a diagnosis of chronic fatigue syndrome [1,2].

Chronic fatigue syndrome

Chronic fatigue syndrome is a condition of unknown cause characterised mainly by debilitating physical and/or mental tired-

ness. There are no physical signs and no confirmatory laboratory tests. The diagnosis is made, therefore, by excluding other causes (thyroid disease, anaemia etc.) and rests on patients satisfying a number of other symptom criteria as well as having fatigue [1,2]. Many of these symptoms, including fatigue, however, are also seen in IIH [3–6] often in sufficient measure in individual patients to qualify them, otherwise, for a diagnosis of chronic fatigue syndrome. Signs of raised intracranial pressure, therefore, protect a patient with IIH from being diagnosed with chronic fatigue syndrome. What if these signs were absent, however, as they nearly always would be in IIHWOP or in IIH with neither papilloedema nor headache? What would prevent these patients being diagnosed with chronic fatigue syndrome if they fulfilled the requisite clinical criteria? Nothing, unless there were reason to measure intracranial pressure directly.

We have tested this point in a small number of patients (n = 20) diagnosed with chronic fatigue syndrome (in whom headache was a prominent symptom) and found that 10% had unequivocal IIH according to current criteria – specifically IIHWOP – when it was sought out with lumbar puncture [11]. We also found that the mean CSF pressure in the group (19 cm H₂O) was towards the high end of normal. More importantly, we found that, regardless of whether the opening pressure matched IIH criteria, when intracranial pressure was reduced by drainage of CSF, 85% of patients reported an amelioration of symptoms, including fatigue [12]. This is a key factor in deciding whether headache is caused by abnormally raised intracranial pressure [15]. It is a small step to use it to decide whether other symptoms, such as fatigue, are also related to intracranial pressure.

The CSF pressure readings in the majority of these patients, therefore, and their clinical response to CSF drainage invite consideration of another category of illness, one in which there is a disorder of intracranial pressure similar to IIH but which fails to match the IIH criteria on almost all counts, one of whose clinical manifestations is chronic fatigue syndrome. This would essentially be IIH without papilloedema or intracranial hypertension and raises the possibility, not just that IIH is being missed in cases of chronic fatigue syndrome, but that the two conditions are related.

Clearly, there have to be a strong caveats to this work, which was an audit of clinical practice, involving a select group of patients with headache, rather than a controlled clinical trial and takes no account of observer bias or any placebo effect of lumbar puncture. Nevertheless, the pick-up rate for unequivocal IIH accords well with the prevalence of unsuspected IIH in patients with other headache syndromes [16–18]. Moreover, bias and the placebo effect of lumbar puncture would have to be very strong indeed to account completely for the recorded response to CSF drainage.

Observations on the epidemiology of IIH and chronic fatigue syndrome

The population incidence of IIH is about 1 per 100,000 per year [3,7]. Given the known or calculated relative frequencies of the other forms of IIH, therefore, the prevailing wisdom would have it that IIH without headache must have an incidence of 0.1 per 100,000, IIHWOP an incidence of 0.05 per 100,000 and IIH without papilloedema or headache an incidence of 0.005 per 100,000. If IIH without papilloedema or raised intracranial pressure exists, this would have to be rarer still (Table 1). Yet, as already mentioned, this is an inversion of the normal hierarchy of chronic disease states, placing the severest form of a condition as the most common. It has to be questioned.

The population incidence of chronic fatigue syndrome is about 235 per 100,000 per year [14]. About 75% of patients with chronic

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