New horizons for Idiopathic intracranial hypertension

Mollan, Susan; Grech, Olivia; Alimajstorovic, Zerin; Wakerley, Benjamin; Sinclair, Alex

DOI:
10.1093/bmb/ldaa034

Document Version
Peer reviewed version

Citation for published version (Harvard):
Mollan, S, Grech, O, Alimajstorovic, Z, Wakerley, B & Sinclair, A 2020, 'New horizons for Idiopathic intracranial hypertension', *British Medical Bulletin*. https://doi.org/10.1093/bmb/ldaa034

New horizons for Idiopathic intracranial hypertension

Susan P Mollan FRCOphth[1], Olivia Grech, MRes[2,3], Zerin Alimajstorovic PhD[2,3], Benjamin R Wakerley FRCP PhD [5], Alexandra J Sinclair PhD[2,3,4]

1 Birmingham Neuro-Ophthalmology, Queen Elizabeth Hospital, Birmingham, United Kingdom, UK.

2 Metabolic Neurology, Institute of Metabolism and Systems Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, B15 2TT, UK.

3 Centre for Endocrinology, Diabetes and Metabolism, Birmingham Health Partners, Birmingham, B15 2TH, UK.

4 Department of Neurology, University Hospitals Birmingham NHS Foundation Trust, Queen Elizabeth Hospital, Birmingham, B15 2WB, UK.

5 Department of Neurology, Gloucestershire Royal Hospital, Gloucester, UK

S Mollan, soozmollan@doctors.org.uk http://orcid.org/0000-0002-6314-4437

O Grech oxg958@student.bham.ac.uk https://orcid.org/0000-0001-5560-802X

Z Alimajstorovic z.alimajstorovic@bham.ac.uk http://orcid.org/0000-0001-5622-8301

B Wakerley, benwakerley@fastmail.fm https://orcid.org/0000-0003-1016-5207

A Sinclair, a.b.sinclair@bham.ac.uk http://orcid.org/0000-0003-2777-5132

Corresponding Author- Professor Alexandra J Sinclair: a.b.sinclair@bham.ac.uk

Title Character count: 48 (without spaces) 53 (with)

Abstract Word count: 150

Manuscript Words Total: 2,683

Declarations

Funding

AS is funded by a Sir Jules Thorn Award for Biomedical Science

OG is funded by a Brain Research UK PhD Studentship

Conflicts of interest

SPM - Invex therapeutics advisory board (2019); Heidelberg engineering speaker fees (2019).

OG – Invex theraputics consultancy work (2020)

ZA –no conflicts of interest in the subject matter to declare.

BRW- Invex therapeutics consultancy fees (2020).

ASJ - ASJ - Invex therapeutics, company director with salary and stock options (2019, 2020).

Acknowledgements

Figure was created using Biorender.com

Data Availability Statement

No new data were generated or analysed in support of this review.

Abstract

Introduction

Idiopathic intracranial hypertension (IIH) is becoming a recognised condition due to the increasing incidence linked to a global obesity epidemic.

Sources of data

All English papers on PubMed, Cochrane and Scholar between inception until March 1st, 2020 were considered.

Areas of agreement

Studies suggest central adiposity has a pathogenic role. Recent weight gain is a risk factor and weight loss has a key role in management.

Areas of controversy

Interpretation of abnormal lumbar puncture opening pressure is debated. There is an increasing recognition of obesity stigma and how this should be approached.

Growing points

Further evidence is required for the choice of surgical intervention for fulminant IIH. Education regarding IIH should be evidence based.

Areas timely for developing research.

Novel research of the pathology of IIH is influencing development of therapies such as glucagon-like peptide-1 receptor agonists and targeting unique androgen signatures. The newly discovered cardiovascular risk requires further attention.

KEY WORDS: Idiopathic intracranial hypertension; pseudotumor cerebri; papilloedema; headache; obesity; androgens; GLP-1; raised intracranial pressure

Introduction

The first consensus guidelines for investigation and management of idiopathic intracranial hypertension (IIH), also known as pseudotumour cerebri, were published in 2018.[1] The aim was to produce a clear systematic approach to diagnosing IIH, exclude other causes and provide a framework for management to standardise care between neurologists, ophthalmologists and neurosurgeons. One of the reasons for the commissioning of this guideline was the increased awareness of IIH and that clinicians felt they were managing more people with IIH. This has subsequently been reflected in a number of studies that have documented a substantial increase in the incidence and prevalence of the disease in the developed world, linked to the global obesity epidemic. [2, 3] Indeed in the United Kingdom the incidence grew by 108% from 2002 to 2016 from 3.5 per 100,000 to 7.69 per 100,000 in the female population.[2] Within this period there was over 440% rise in admissions to hospital (this included visits to accident and emergency and inpatient admissions). Understanding the current principles of diagnosis and management of IIH is therefore important to many different specialties.

A diagnosis of IIH is based on the presence of papilleodema, with an absence of secondary causes and raised cerebrospinal fluid (CSF) pressure >25 cm CSF, measured by lumbar puncture (LP) in the left lateral decubitus position, and normal CSF constituents.[1] For clinicians there is an accepted underlying pathological role of obesity in IIH.[4] This poses a challenge in how to approach weight management for both the clinician and the patient, and dissipating the stigma of obesity. Alternative medical options are limited with only two randomised control trials investigating acetazolamide.[5] For those with urgent sight threatening disease the type of surgical management varies based on surgical experience although it mainly involves CSF shunting or optic nerve sheath fenestration.[6] Venous sinus stenting is used in some specialist centres although long-term efficacy data are awaited. [7]

This review provides an overview for the consensus guidelines for the investigation of papilloedema and confirming a diagnosis of IIH, as a diagnosis of exclusion. The review challenges the methodology to diagnose papilloedema, the interpretation of the lumbar puncture (LP) opening pressure (OP) and the challenges of dissipating obesity stigma. It exposes areas that require progress including tolerated and safe medical and surgical treatments. It describes the new potential pathogenic mechanisms in this disease, and their potential for targeted therapies (figure 1).

Diagnosing IIH

IIH is characterised by the presence of optic nerve head swelling, normal neuroimaging and raised intracranial pressure (ICP) as measured by LP in the lateral decubitus position.[1] Symptoms of IIH include chronic headaches which severely impacts quality of life [8]; pulsatile tinnitus, back and radicular pain, dizziness, cognitive disturbances and diplopia. [1, 9] Transient visual obscurations are also common and in individual cases there is a risk of permanent visual loss.[10] The major issue with IIH is that not only is it a diagnosis of exclusion, the symptoms can be found in a general headache population and therefore are not pathognomonic.[11]

Identification of papilloedema is not always straight forward and has been found to be the predominant reason for misdiagnosis in IIH. [1, 9, 12] The consensus guidelines suggest that where there is diagnostic uncertainty, an eye examination should be performed by a specialist who is confident in diagnosing papilloedema.[1] Malignant hypertension (diastolic blood pressure ≥120 mmHg or systolic blood pressure ≥ 180 mmHg) should be excluded then neuroimaging performed. This can be a CT or MRI but must include venography. Missed cerebral venous sinus thrombosis carries a significant morbidity and has a completely different management approach and therefore should be excluded as a priority.[13]

Neuroimaging features of raised ICP include the CT scan showing more slit like ventricles and the MRI highlighting orbital scleral flattening; widening of the perioptic spaces; flattening of the anterior pituitary resulting in a partial or complete empty sella and venous sinus stenosis. Bidot et al[14] calculated the sensitivity of the presence of an empty sella in IIH as ranging from 65% to 80%, depending on the definition used. A completely empty sella with lack of visible pituitary gland was found to be uncommon and reported in less than 10% of cases.[14] In isolation no individual MRI feature of raised ICP had sufficient specificity to be diagnostic of raised ICP and can be incidental. Reduced pituitary gland height (less than 4.8mm) was moderately sensitive at 80% but had a low specificity of 64%.[15] In addition no single MRI characteristics associated with IIH have been found to be predictive of visual outcomes.[16]

When no structural cause of raised ICP is identified, the patient can then undergo LP. The LP OP is measured in the lateral decubitus position and if possible, the patient should extend their legs. Valsalva, breath holding and hyperventilation should be minimised as they may temporarily increase the ICP measure, and putting the patient at ease should reduce their anxiety.[17] The use of ultrasound is recommended for LP as it can be challenging in obese patients.[1] X-ray guided LPs can be used if the attempt is unsuccessful, however it is important for the interventional neuroradiologist or anaesthetist to be informed of the critical importance of measuring the OP in the correct position and not sitting.[18] Should the LP OP be expectantly different from the clinical picture, a re-assessment

may be necessary. A formal diagnosis of IIH requires CSF OP to be greater than 25cm CSF and the contents of the CSF to be normal. Recently as part of the consensus guidelines[1], many different specialists (neurologists, neurosurgeons and neuro-ophthalmologists) were asked to consider the level at which they clinically determined that the LP OP was pathological, this ranged from 25 to 30cm CSF (figure 1). Currently there is no evidence as to how much CSF should be removed or what the closing pressure should be. There is significant anxiety regarding LP [17], known complications and a common risk of low pressure headache. Any improvement in headache following LP is small and short lived [19], and the guidelines do not recommend repeated LPs for therapeutic means in typical IIH. [1]

Exclusion of other causes of papilloedema is essential, as many conditions such as the previous mentioned CVST, anaemia[20], obstructive sleep apnoea and drug causes which may be rectified. The literature is clear regarding fluoroquinolones[21], vitamin A analogues[22], and tetracyclines[23], all of which have been reported to cause raised ICP in some patients. Many more may have casual associations.[1] Often women are incorrectly counselled regarding the association of the use of the oral contraceptive pill; there is no high-quality evidence to suggest that modern oral contraceptives (with much lower oestrogen content) have a direct relationship with IIH. Frequently there may be an association with weight gain, when commencing the oral contraceptive or indeed mood disorder drugs.

With the investigations complete, the consensus guidelines defines “typical” IIH as those individuals who are female, of childbearing age and who have a body mass index (BMI) greater than 30 kg/m^2; and “atypical” IIH as those who are not female, or not of childbearing age or who have a BMI below 30 kg/m^2. These atypical patients require more in-depth investigation to ensure no other underlying causes and often a careful revision to the exclude drug related causes.

Approaching obesity in IIH

Obesity is now recognised as a relapsing and remitting disease driven by complex pathophysiological factors including genetic, biological and environmental. As IIH occurs predominantly in women, who are overweight or obese[2, 3] many investigators have investigated this risk through study. Those with a body mass index (BMI) under 30 kg/m^2 (non-obese) who gained a moderate amount of weight, were more likely to develop IIH compared to people with similar BMI whose weight was stable; this study also reported that between a 5% to 15% weight gain increased the risk of developing IIH.[24] A prospective weight loss study used a very low-calorie diet to induce significant weight loss of

approximately 15%; this resulted in a significantly lower ICP, improvement in the papilloedema and visual function. Headache frequency and severity was halved with a paralleled reduction in analgesic use.[25] Weight loss specifically from the truncal region induced remission and indeed truncal fat mass correlated with ICP, as measured by LP.[26] The optimal method of sustained weight loss, lifestyle intervention, pharmacotherapy or surgery, has yet defined either for obesity or for IIH. Permanent weight loss for IIH is important as weight gain of 6% has led, in some, to recurrence of the disease.[27] It is well known that sustained weight loss is difficult to achieve with lifestyle interventions alone, as on average, patients regain one-third to one-half of the weight that was lost at 12 months, and return to their original weight within 5 years.[28] The IIH: weight trial aspires to address some of these issues for IIH where participants were randomised to either a community weight loss programme or bariatric surgery pathway.[29]

Following IIH diagnosis, sensitive and appropriate weight management counselling should be undertaken for all patients with a BMI >30kg/m^2.[1] Obesity stigma amongst health care professionals and patients has been documented to significantly obstruct progress and is associated with poorer patient outcomes.[30] Education and understanding may help to overcome this significant barrier in IIH.

Emergency treatment for visual loss in IIH

The key second principle of IIH management is to protect vision. If there is a risk of visual loss, the emergency management is surgical typically by means of CSF diversion or optic nerve sheath fenestration (ONSF).[1] Where surgery is delayed due to operational reasons a temporary lumbar drain should be sited to protect the vision.[1] Recent advances in CSF shunting include antibiotic impregnated shunts and adjustable anti-siphon and gravity valves aimed at reducing the risk of low pressure headaches. There are reportedly fewer complications with ONSF than CSF shunting and the procedure is used widely in Europe and USA, however the case series are small and further research is required.[31] Due to the anatomical abnormalities of the cerebral venous sinus system in IIH patients, neurovascular stenting is now used by some groups improve IIH symptoms. However, the evidence base is not yet established with no long-term efficacy or safety trials to inform routine clinical practice.[1, 7]

Managing symptoms of IIH

Acetazolamide is the most commonly used medicine prescribed for IIH, and like other drugs has been used off-label. The 2015 Cochrane review on IIH management found an absence of evidence to recommend or reject the efficacy of treatments currently available. Just two trials met the inclusion criteria, both of which assessed acetazolamide against placebo. [32] The IIH-Treatment Trial (IIHTT) described a small improvement in visual field function in patients with mild visual loss following acetazolamide (up to 4g daily) treatment in conjunction with a low-sodium weight-reduction diet in IIH patients.[33] However, Ball *et al* had previously reported 48% of IIH patients discontinued acetazolamide (1.5g daily) use due to adverse effects and the earlier study failed to show any treatment effect.[34] In light of this limited evidence not all UK clinicians prescribe the drug for IIH due to its side effect profile and patient choice.[1] Both studies recommended weight loss alongside their interventions, so untangling the role of the drug overweight lost is difficult.[35]

Scotton *et al*. evaluated the following drugs reportedly used for IIH: acetazolamide, topiramate, amiloride, octreotide and furosemide. These medications were trialled *in vivo* at clinically relevant doses equivalent to human doses of acetazolamide 4000g, topiramate 200mg, amiloride 20mg, octreotide 2mg and furosemide 240mg. The result showed topiramate significantly reduced ICP.[36] This was encouraging as topiramate was previously investigated in a small open label IIH study, patients were observed to improve but the lack of a placebo group limits interpretation.[37] The side effects of topiramate include nausea and anorexia, and for the minority it can also cause cognitive symptoms, low mood and is also known to reduce the efficacy of the oral contraceptive. Both the animal and the prospective human study indicate that Topiramate may be a suitable medication for further investigation in clinical studies to reduce ICP and headache morbidity in IIH.

Reducing headache disability is a key aim for the patients.[38] Initially the headache phenotype should be assessed, most commonly this is a migraine-like headache (migraine is a primary headache disorder in the ICHD ordinarily excluding it where headache is due to IIH).[39] Other phenotypes reported include IIH headache, medication-overuse headache, tension-type headache, low CSF pressure headache and headache attributed to iatrogenic Chiari malformation secondary to CSF shunting.[39, 40] Expert opinion currently manages the headache in IIH along the treatment principles of the analogous primary headache disorder.[1, 40] There is one open label study that investigated the use of topiramate[37], aside this there is no direct evidence to support the optimal management of

headaches in IIH.[1] Like many other headache disorders, IIH patients must be informed of the risk of medication overuse headaches. If there is evidence of medication overuse, then withdrawal of medication is necessary. [41] Acute and preventative strategies that are used for migraine are recommended including triple therapy as per UK NICE guidance[42] (triptan with paracetamol or a nonsteroidal anti-inflammatory and antiemetic medication). As the pattern of headache changes over time in IIH patients, careful re-assessment is necessary. Clearly more investment in headache treatments is an unmet clinical need, as headache improvement is a key driver for improved quality of life in IIH.[8]

New understanding of IIH

There have been several advances in the understanding of the underlying pathophysiology of IIH. [43] After sequential proof of concept laboratory research, glucagon like protein -1 (GLP-1) inhibition was shown to reduce ICP. The GLP-1 receptor (GLP-1R) was demonstrated to be present in the choroid plexus; then a GLP-1R agonist was shown to reduce Na^+-K^+-ATPase activity (which drives CSF production) and so lower CSF secretion and ICP in vivo [44]

This is exciting as GLP-1R agonists are used for diabetes (exenatide, liraglutide, lixisenatide, semaglutide, albiglutide, dulaglutide) and to manage obesity (liraglutide, semaglutide). GLP-1R agonists stimulate secretion of insulin, without causing hypoglycaemia, suppress glucagon secretion and delaying gastric emptying and also have the additional benefits of inducing weight loss though hypothalamic signalling, which promotes satiety and decreases food intake. For IIH there may be additional benefits as pathologically elevated ICP can be reduced by nearly 50% in rats treated with exenatide, with effects sustained for up to 2 weeks.[44] This marked reduction of ICP was not seen when the clinically relevant doses of current IIH therapies acetazolamide, amiloride, octreotide and fruosemide were investigated.[36] Given known clinical data, weight loss takes time to achieve, however both the in vivo study and that of human GLP-1R agonists show beneficial effects within two weeks.[45] These highlight that it is the gut neuropeptide axis and metabolic factors underpinning these results, rather than a simplistic answer of “obesity’.

Another piece of the jigsaw in the metabolic story is androgen excess. There is a known increased incidence of polycystic ovarian disease (PCOS) in IIH patients.[1] Androgen production is reduced following weight loss in IIH patients.[46] Additionally, IIH presents earlier in those IIH patients who

have androgen excess. However, a recent study describes women with IIH as having higher active CSF testosterone than in women with PCOS or simple obesity.[47] Functionally, testosterone has been described to increase ICP.[48] Further studies in vivo of a choroid plexus cell line showed that testosterone increases Na^+-K^+-ATPase activity, a surrogate of CSF secretion.[47] A diagnosis of IIH secondary to testosterone therapy in transgender patients has been reported [48], where symptoms and signs resolved with the withdrawal of testosterone.[48] Pursuing specific androgens could be another therapeutic target for IIH.

Emerging theme of increased risk of cardiovascular disease

A recent population-based longitudinal cohort study of IIH in the UK reported that IIH, independent of obesity, is a risk factor for cardiovascular disease in women.[3] This suggests underlying metabolic dysregulation, over and above what is caused by obesity. Further work is required to understand whether clinical practice should change to include primary prevention of cardiovascular disease to modify the long-term morbidity.

Conclusion

The current IIH consensus guidelines are aimed at helping to improve and standardise care. The advances in our understanding of IIH shows that it is not just a disease of increased ICP, headache and visual loss but a metabolic disease that has broad manifestations including cardiovascular disease. The advances in the pathophysiology of IIH is paving the way for controlled trials in directed therapies such as GLP-1R agonists and potential specific androgen targets.

References

1. Mollan SP, Davies B, Silver NC, et al. Idiopathic intracranial hypertension: consensus guidelines on management. Journal of neurology, neurosurgery, and psychiatry 2018;89:1088-1100.
2. Mollan SP, Aguiar M, Evison F, Frew E, Sinclair AJ. The expanding burden of idiopathic intracranial hypertension. Eye (Lond) 2018;33:478-485.
3. Adderley NJ, Subramanian A, Nirantharakumar K, et al. Association Between Idiopathic Intracranial Hypertension and Risk of Cardiovascular Diseases in Women in the United Kingdom. JAMA Neurol 2019;76:1088-1098.
4. Andrews LE, Liu GT, Ko MW. Idiopathic Intracranial Hypertension and Obesity. Hormone Research in Paediatrics 2014;81:217-225.
5. Piper RJ, Kalyvas AV, Young AM, Hughes MA, Jamjoom AA, Fouyas IP. Interventions for idiopathic intracranial hypertension. Cochrane Database Syst Rev 2015:Cd003434.
6. Kalyvas A, Neromyliotis E, Koutsarnakis C, et al. A systematic review of surgical treatments of idiopathic intracranial hypertension (IIH). Neurosurgical Review 2020.
7. Gurney SP, Ramalingam S, Thomas A, Sinclair AJ, Mollan SP. Exploring The Current Management Idiopathic Intracranial Hypertension, And Understanding The Role Of Dural Venous Sinus Stenting. Eye Brain 2020;12:1-13.
8. Mulla Y, Markey KA, Woolley RL, Patel S, Mollan SP, Sinclair AJ. Headache determines quality of life in idiopathic intracranial hypertension. The journal of headache and pain 2015;16:521-521.
9. Mollan SP, Hornby C, Mitchell J, Sinclair AJ. Evaluation and management of adult idiopathic intracranial hypertension. Pract Neurol 2018;18:485-488.
10. Best J, Silvestri G, Burton B, Foot B, Acheson J. The Incidence of Blindness Due to Idiopathic Intracranial Hypertension in the UK. The open ophthalmology journal 2013;7:26-29.
11. Yri HM, Jensen RH. Idiopathic intracranial hypertension: Clinical nosography and field-testing of the ICHD diagnostic criteria. A case-control study. Cephalalgia 2015;35:553-562.
12. Fisayo A, Bruce BB, Newman NJ, Biousse V. Overdiagnosis of idiopathic intracranial hypertension. Neurology 2016;86:341-350.
13. Bentley JN, Figueroa RE, Vender JR. From presentation to follow-up: diagnosis and treatment of cerebral venous thrombosis. Neurosurgical focus 2009;27:E4.
14. Bidot S, Saindane AM, Peragallo JH, Bruce BB, Newman NJ, Biousse V. Brain Imaging in Idiopathic Intracranial Hypertension. J Neuroophthalmol 2015;35:400-411.
15. Mallery RM, Rehmani OF, Woo JH, et al. Utility of Magnetic Resonance Imaging Features for Improving the Diagnosis of Idiopathic Intracranial Hypertension Without Papilledema. J Neuroophthalmol 2019;39:299-307.

16. Saindane AM, Bruce BB, Riggeal BD, Newman NJ, Biousse V. Association of MRI findings and visual outcome in idiopathic intracranial hypertension. AJR Am J Roentgenol 2013;201:412-418.

17. Scotton WJ, Mollan SP, Walters T, et al. Characterising the patient experience of diagnostic lumbar puncture in idiopathic intracranial hypertension: a cross-sectional online survey. BMJ Open 2018;8:e020445.

18. Wright BL, Lai JT, Sinclair AJ. Cerebrospinal fluid and lumbar puncture: a practical review. J Neurol 2012;259:1530-1545.

19. Yiangou A, Mitchell J, Markey KA, et al. Therapeutic lumbar puncture for headache in idiopathic intracranial hypertension: Minimal gain, is it worth the pain? Cephalalgia 2019;39:245-253.

20. Mollan SP, Ball AK, Sinclair AJ, et al. Idiopathic intracranial hypertension associated with iron deficiency anaemia: a lesson for management. Eur Neurol 2009;62:105-108.

21. Sodhi M, Sheldon CA, Carleton B, Etminan M. Oral fluoroquinolones and risk of secondary pseudotumor cerebri syndrome: Nested case-control study. Neurology 2017;89:792-795.

22. Libien J, Kupersmith MJ, Blaner W, et al. Role of vitamin A metabolism in IIH: Results from the idiopathic intracranial hypertension treatment trial. Journal of the neurological sciences 2017;372:78-84.

23. Kesler A, Goldhammer Y, Hadayer A, Pianka P. The outcome of pseudotumor cerebri induced by tetracycline therapy. Acta Neurologica Scandinavica 2004;110:408-411.

24. Daniels AB, Liu GT, Volpe NJ, et al. Profiles of obesity, weight gain, and quality of life in idiopathic intracranial hypertension (pseudotumor cerebri). Am J Ophthalmol 2007;143:635-641.

25. Sinclair AJ, Burdon MA, Nightingale PG, et al. Low energy diet and intracranial pressure in women with idiopathic intracranial hypertension: prospective cohort study. Bmj 2010;341:c2701.

26. Hornby C, Botfield H, O'Reilly MW, et al. Evaluating the Fat Distribution in Idiopathic Intracranial Hypertension Using Dual-Energy X-ray Absorptiometry Scanning. Neuro-ophthalmology (Aeolus Press) 2017;42:99-104.

27. Ko MW, Chang SC, Ridha MA, et al. Weight gain and recurrence in idiopathic intracranial hypertension: a case-control study. Neurology 2011;76:1564-1567.

28. Dombrowski SU, Knittle K, Avenell A, Araújo-Soares V, Sniehotta FF. Long term maintenance of weight loss with non-surgical interventions in obese adults: systematic review and meta-analyses of randomised controlled trials. BMJ : British Medical Journal 2014;348:g2646.

29. Ottridge R, Mollan SP, Botfield H, et al. Randomised controlled trial of bariatric surgery versus a community weight loss programme for the sustained treatment of idiopathic intracranial

hypertension: the Idiopathic Intracranial Hypertension Weight Trial (IIH:WT) protocol. BMJ Open 2017;7:e017426.

30. Puhl RM, Heuer CA. Obesity stigma: important considerations for public health. Am J Public Health 2010;100:1019-1028.

31. Spitze A, Malik A, Al-Zubidi N, Golnik K, Lee AG. Optic nerve sheath fenestration vs cerebrospinal diversion procedures: what is the preferred surgical procedure for the treatment of idiopathic intracranial hypertension failing maximum medical therapy? J Neuroophthalmol 2013;33:183-188.

32. Piper RJ, Kalyvas AV, Young AMH, Hughes MA, Jamjoom AAB, Fouyas IP. Interventions for idiopathic intracranial hypertension. Cochrane Database of Systematic Reviews 2015.

33. Wall M, Kupersmith MJ, Kieburtz KD, et al. The idiopathic intracranial hypertension treatment trial: clinical profile at baseline. JAMA Neurol 2014;71:693-701.

34. Ball AK, Howman A, Wheatley K, et al. A randomised controlled trial of treatment for idiopathic intracranial hypertension. Journal of Neurology 2011;258:874-881.

35. Mollan SP, Burdon MA, Sinclair AJ. Treating idiopathic intracranial hypertension. JAMA Neurol 2014;71:1326-1327.

36. Scotton WJ, Botfield HF, Westgate CS, et al. Topiramate is more effective than acetazolamide at lowering intracranial pressure. Cephalalgia 2019;39:209-218.

37. Celebisoy N, Gokcay F, Sirin H, Akyurekli O. Treatment of idiopathic intracranial hypertension: topiramate vs acetazolamide, an open-label study. Acta Neurol Scand 2007;116:322-327.

38. Mollan S, Hemmings K, Herd CP, Denton A, Williamson S, Sinclair AJ. What are the research priorities for idiopathic intracranial hypertension? A priority setting partnership between patients and healthcare professionals. BMJ Open 2019;9:e026573.

39. Mollan SP, Hoffmann J, Sinclair AJ. Advances in the understanding of headache in idiopathic intracranial hypertension. Curr Opin Neurol 2019;32:92-98.

40. Friedman DI, Rausch EA. Headache diagnoses in patients with treated idiopathic intracranial hypertension. Neurology 2002;58:1551-1553.

41. Wakerley BR. Medication-overuse headache: painkillers are not always the answer. Br J Gen Pract 2020;70:58-59.

42. NICE. Clinical Guideline (150): Headaches: diagnosis and management of headaches in young people and adults. Surveillance report [online]. Available at: https://www.nice.org.uk/guidance/cg150/resources/headaches-surveillance-review-document2. Accessed 21/05/2020.

43. Hornby C, Mollan SP, Botfield H, O'Reilly MW, Sinclair AJ. Metabolic Concepts in Idiopathic Intracranial Hypertension and Their Potential for Therapeutic Intervention. Journal of neuro-ophthalmology : the official journal of the North American Neuro-Ophthalmology Society 2018;38:522-530.

44. Botfield HF, Uldall MS, Westgate CSJ, et al. A glucagon-like peptide-1 receptor agonist reduces intracranial pressure in a rat model of hydrocephalus. Science translational medicine 2017;9.

45. Dushay J, Gao C, Gopalakrishnan GS, et al. Short-term exenatide treatment leads to significant weight loss in a subset of obese women without diabetes. Diabetes Care 2012;35:4-11.

46. Sinclair AJ, Walker EA, Burdon MA, et al. Cerebrospinal fluid corticosteroid levels and cortisol metabolism in patients with idiopathic intracranial hypertension: a link between 11beta-HSD1 and intracranial pressure regulation? The Journal of clinical endocrinology and metabolism 2010;95:5348-5356.

47. O'Reilly MW, Westgate CS, Hornby C, et al. A unique androgen excess signature in idiopathic intracranial hypertension is linked to cerebrospinal fluid dynamics. JCI insight 2019.

48. Hornby C, Mollan SP, Mitchell J, et al. What Do Transgender Patients Teach Us About Idiopathic Intracranial Hypertension? Neuro-ophthalmology (Aeolus Press) 2017;41:326-329.