UNIVERSITY^{OF} BIRMINGHAM University of Birmingham Research at Birmingham

Current and emerging diagnostic and management approaches for idiopathic intracranial hypertension

Piccus, Ravi; Thaller, Mark; Sinclair, Alex; Mollan, Susan

DOI: 10.1080/14737175.2023.2206567

License: Creative Commons: Attribution-NonCommercial (CC BY-NC)

Document Version Peer reviewed version

Citation for published version (Harvard):

Piccus, R, Thaller, M, Sinclair, A & Mollan, S 2023, 'Current and emerging diagnostic and management approaches for idiopathic intracranial hypertension', *Expert Review of Neurotherapeutics*. https://doi.org/10.1080/14737175.2023.2206567

Link to publication on Research at Birmingham portal

Publisher Rights Statement:

This is an Accepted Manuscript of an article published by Taylor & Francis in Expert Review of Neurotherapeutics on 28/4/2023, available at: https://doi.org/10.1080/14737175.2023.2206567

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

•Users may freely distribute the URL that is used to identify this publication.

•Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.

•User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?) •Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

Abstract

Introduction

Idiopathic Intracranial Hypertension is characterised by raised intracranial pressure that triggers disabling headaches and can cause permanent visual loss. There is an increased incidence and prevalence of the condition linked to location specific obesity rates. There are no licensed treatments for the condition. The majority of approaches to managing the disease prioritize resolution of papilloedema. However, evidence is emerging that Idiopathic Intracranial Hypertension is a systemic metabolic disease.

Areas covered

The aim of this review is to present the emerging pathophysiology evidence which is leading to novel targeted therapeutics. The diagnostic pathway is outlined. The current and potential management approaches for idiopathic intracranial hypertension are also discussed.

Expert opinion

Idiopathic intracranial hypertension is a condition with metabolic dysregulation with systemic manifestations that are present over and above what can be explained by obesity alone. While most of the current management of this condition focuses on the eyes, future management needs to address the disabling headaches and the systemic risks of preeclampsia, gestational diabetes and major cardiovascular events.

Keywords

Bariatric surgery; glucagon like peptide 1; headache; intracranial pressure; optical coherence tomography; papilloedema; pregnancy; prognosis; pseudotumor cerebri; vision.

Expert commentary

1. Introduction

Idiopathic intracranial hypertension (IIH) is a condition of raised intracranial pressure (ICP) that can cause permanent optic nerve damage [1]. The epidemiology of the disease shows high prevalence in obese women of childbearing age, the incidence is increasing following obesity trends [2,3] and it predominately affects those who are socioeconomically deprived [3,4,5]. The symptoms of raised ICP are most commonly migraine-like headaches, visual obscurations, pulsatile tinnitus and cognitive impairment [6]. Pathophysiology of the disease is due to altered CSF secretion homeostasis, metabolic imbalance and possible anatomical differences [7]. Diagnosis is based on the revised diagnostic criteria and on excluding secondary causes of intracranial hypertension [8]. The principles of IIH management involve sight preservation, symptom control and targeting the underlying aetiology [9].

2. Aims and Methods

The aim of this commentary was to outline the current understanding of the pathophysiology, diagnosis and management of IIH. This review also aimed to address the frontiers of IIH, namely the new role of metabolic targets of the disease, namely 11βhydroxysteroid dehydrogenase-1 (11β-HSD1) antagonists and Glucagon Like Peptide-1 (GLP-1) agonism. To support this, a detailed search of the scientific literature included all English language papers on PubMed, Cochrane and Google Scholar between inception until December 1st, 2022, combining free-text and controlled vocabulary terms for IIH. Key words included idiopathic intracranial hypertension; intracranial pressure; headache; obesity; optical coherence tomography; papilloedema; pseudotumour cerebri; randomized control trial; surgery; shunting; stenting; venous sinus stenosis; vision and weight loss.

3. Incidence and prevalence

Whilst IIH is considered a rare condition, the global prevalence has significantly increased in the last decade [10]. Meta-analysis including data from ten countries reported a pooled IIH incidence of 1.2 per 100,000 per year with a higher prevalence being directly associated with national prevalence of obesity [10]. The majority of people diagnosed with IIH are

reproductive aged women living with obesity [4,11,12]. Importantly, a correlation of the disease and social deprivation has been found in the UK and USA [3,4,12-14].

The prevalence of IIH in children has been reported as 0.71 per 100,000. When stratified by age, significant differences between male and female prevalence only existed from age 7 onwards [15]. In the 12–15-year-old subgroup the prevalence was 4.18 per 100,000 in males versus 10.7 per 100,000 in females. Obesity was considered a risk factor in paediatric cases similarly to adults [16], and a recent review has highlighted that post-pubertal IIH has a similar phenotype to adult IIH [17].

4. Pathophysiology

The pathophysiology of IIH is attributed to altered cerebrospinal fluid (CSF) dynamics, resulting in raised ICP [18,19]. CSF is secreted by the choroid plexus and drained via the arachnoid granulations to the dural venous sinuses [20]; and there is an increasing recognition of the role of the lymphatics and glymphatic system CSF absorption [21,22].

4.1 Choroid Plexus

The choroid plexus is responsible for CSF secretion and it is accepted that transport proteins orchestrate the unidirectional flux of ions and water that constitutes the CSF secretion [20,23,24]. These proteins generate an osmotic gradient which induces net water movement. Fluid secretion by these cells involves the sodium–potassium ATPase pump (Na⁺-K⁺-ATPase), epithelial sodium channel, chloride channel and aquaporin-1 water channel (AQP-1). They cause the efflux of Na⁺, K⁺, chloride, bicarbonate and water into the CSF [20,23,24].

Androgen receptors are expressed in the choroid plexus and it also contains key enzymes to generate and metabolize androgens [25]. Testosterone has been found to significantly enhanced the activity of Na⁺/K⁺ ATPase pump. Therefore, the excess androgens that have been found in IIH have been postulated to modulate CSF secretion via the choroid plexus [25,26].

AQP1 appears to be important in drug-induced elevation of ICP [27], and animal studies show a link between obesity, AQP1 expression and raised ICP [28]. However, there is yet to be an evaluation of the role of AQP1 in IIH in humans.

4.2 Anatomical

Delayed glymphatic drainage, particularly in the frontal and temporal regions of the brain, has been found to be responsible for impaired CSF flow in IIH [21]. Structural analysis of the glial-neuro-vascular interface in IIH patients has shown increased astrocyte GFAP immunoreactivity, patchy astrogliosis and loss of astrocyte domains [29]. Astrocytic mitochondrial dysfunction has been suggested as a key factor in impaired glymphatic drainage [29].

Cerebral venous sinus stenosis is a common feature of IIH [30,31,32]. Stenosis is mostly due to extrinsic pressure in IIH indicating consequence rather than causality of raised ICP [32]. Advances in imaging that allow characterisation of the internal sinus structure have shown four anatomical variations in IIH: arachnoid granulations, fibrous septa, brain herniations into dural venous sinus and circumscribed stenosis [33]. A feedforward relationship exists wherein stenosis impairs CSF drainage and causes raised ICP, which acts to further compress the venous sinus resulting in further ICP increase [34,35]. Clinically, the degree of venous sinus stenosis does not appear to correlate with the visual outcomes [36,37].

4.3 Metabolic perturbations

Exploration of the link between IIH and obesity has revealed multiple cross-over enzymes with potential pathologic influence in IIH [38]. Comparison of lipid profiles and adipose distribution has shown increased truncal fat and reduced truncal lean mass are associated with leptin excess and insulin resistance in IIH patients [39]. This phenotype of insulin resistance manifests with the increased risk of gestational diabetes and type 2 diabetes mellitus in IIH compared to the general population[4]. Adipose tissue (omental and subcutaneous) has distinct features in IIH compared to age, gender and BMI matched controls [39]. IIH adipose tissue is transcriptionally primed for lipogenesis and calorie intake and is likely of relevance to potentially predisposing patients to gaining adipose mass [39].

Hyperandrogenism is a feature of IIH and it has a unique signature, different from that of obesity and polycystic ovarian syndrome (PCOS), with increased testosterone found in both the CSF and serum [25]. Testosterone increases CSF secretion in vitro, further supporting the role of androgens in the underlying pathogenesis of IIH [28]. Androgen excess has been shown to be metabolically deleterious [40]. Acute androgen exposure has been shown to cause lipogenesis in PCOS [41]. Therefore the presence of hyperandrogenism in IIH is likely to reflect the metabolic phenotype and also provides a clear mechanism for excessive CSF secretion.

The prevalence of PCOS is higher in IIH than in the unaffected general population, suggesting an androgenic effect of raised ICP and obesity in these patients [42,43]. In fact, female IIH patients with androgen excess have been found to develop IIH at an earlier age and female-to-male transgender people have developed IIH after starting testosterone therapy [44,45].

Pro-inflammatory cytokines have been investigated in IIH and found excess interleukin 2, interleukin 17 and chemokine C-C motif ligand 2 in the CSF of IIH patients [38]. Importantly, introduction of these cytokines in lean rats compared to non-treated obese rats has induced similar increases in CSF secretion and impaired drainage, indicating a common inflammatory pathogenesis of CSF dysregulation [46].

Glucocorticoid dysregulation has also been evidenced in IIH. The 11 β -HSD1 is an enzyme which converts inactive cortisone to cortisol and is present in multiple cell types throughout the body including hepatic, adipose and the choroid plexus epithelium [47,48]. 11 β -HSD1 activity is increased in obesity and IIH, however, whilst the hepatic type is dominant in obesity alone, it is the subcutaneous adipose type that is overly active in IIH [49]. Importantly, 11 β -HSD1 activity is associated with leptin and insulin resistance [47] and IIH patients have been shown to have a leptin and insulin resistant phenotype [49]. Changes in 11 β -HSD1 activity do not affect overall cortisol levels, indicating that changes in glucocorticoid signalling are responsible for its metabolic effect [47]. Weight loss is associated with reduced activity of 11 β -HSD1, which is in-turn proportional to ICP reduction and improved cognitive function in IIH [49,50].

5. Diagnostic criteria

The revised criteria to make a diagnosis of IIH [8] outlines signs and symptoms of raised ICP without a known underlying aetiology or secondary cause. For a definite diagnosis of IIH patients need to have papilloedema, normal neurological examination (sixth nerve palsy is allowed), normal neuroimaging (imaging signs of raised ICP are allowed) with venous sinus thrombosis excluded, normal CSF constituents and an elevated opening pressure equal to or above 25cmCSF.

The commonest reported symptom of raised ICP in IIH is a migraine-like headache and this is reflected in the International Headache Society classification (IHS 2013) [11,51,52]. Importantly, headache is reported as moderate-severe with episodic frequency that becomes chronic as the disease progresses [53]. Other symptoms of IIH include pulsatile tinnitus, transient visual obscuration, sixth-nerve palsy and impaired cognitive function [54,55].

5.1 Papilloedema

A diagnostic hallmark of raised ICP is papilloedema, however, papilloedema can be due to other secondary causes that may require expectantly different management to reduce morbidity [56]. Screening and investigations for these are recommended [9]. On detection of papilloedema, emergency referral to a hospital specialist is indicated to initiate a diagnostic pathway outlined in recent IIH consensus guidelines [9] with a full ophthalmic and cranial nerve examination required. Early imaging of the optic nerve head and retina is important not only to distinguish papilloedema from pseudopapilloedema but is helpful for longer term monitoring. Optical coherence tomography (OCT) imaging reveals a number of different findings that can be useful in papilloedema such as retinal nerve fibre layer thickening, retinal and choroidal folds, peripapillary wrinkles and anterior displacement of the lamina cribrosa [57-60].

5.2 Neuroimaging and venography

Once papilloedema is confirmed, urgent brain imaging with CT or MRI with venography are essential [9]. This imaging aims to exclude secondary causes of raised ICP including tumour, infection, hydrocephalus or cerebral venous sinus thrombosis [61]. Cerebral venous sinus thrombosis can lead to venous infarcts, which may result in permanent disability or death, and hence why the importance of dedicated imaging to exclude this [62].

Neuroimaging also identifies characteristics of raised ICP such as partially or empty sella, enlarged optic nerve sheath complex, optic nerve tortuosity, globe flattening, optic nerve head protrusion and venous sinus stenosis [63,64]. Optic canal dimensions do not appear to influence papilloedema grade as measured with CT imaging [65] and MRI findings have not been shown to occur at a higher frequency in those with worst visual outcomes [66]. Recent multivariate analysis of radiographic features indicated that a calculated caudate index, lateral ventricle index and bilateral optic nerve tortuosity were significant predictors of IIH with an r²-value of 0.773 [67]. Other abnormalities with high specificity for the disease are posterior scleral flattening and perioptic subarachnoid space dilatation [68]. In clinical practice MRI findings of raised ICP incidentally found are raising concerns amongst physicians and in one study documented performing lumbar punctures (LP) and starting treatment without necessarily examining for papilloedema first[69].

5.3 Lumbar Puncture

An LP is a necessary criterion for a diagnosis of IIH and confirms absence of other conditions through examination of its constituents [9]. Opening pressure >25 cmCSF is characteristic [8], although 25-30 cmCSF may be normal in some patients [9]. A recent study of LP opening pressure in 35 people with IIH compared to a control population reported the lowest measurement in the IIH group as 29.5cm CSF, with an average of 37.7cm CSF, compared to a control group average of 18.7cmCSF and range of 1-29cmCSF [70]. Some have suggested that LP may be deferred in mild disease of systemically well patients under expert care [71] as LP may cause physical and psychological distress [72,73]. However, in our opinion whilst it is rare that an underlying neoplasm, in the presence of normal MRI imaging, or meningeal inflammation is found, omitting the diagnostic LP can create diagnostic uncertainty both in the present and if there are subsequent relapses.

5.4. Exclusion of secondary causes

As papilloedema is a clinical sign and can be caused by many factors secondary causes need to be excluded. A recent review of secondary intracranial hypertension or secondary

pseudotumor cerebri (sPTC) labelled the patient phenotype in four categories of sPTC of comorbid, medication, infection and hormonal [74]. While it seems like sPTC has been more prevalently recorded in paediatric populations, this is likely due to bias in reporting of paediatric case series [17,74]. Cerebral venous sinus thrombosis is one secondary cause that has already been discussed. Anaemia has been found in one in ten adults referred to a tertiary referral service, and where correction of the anaemia has led to the resolution of symptoms and signs [75]. There have been a number of medicines that have been associated with causing raised ICP and the most common include fluoroquinolones, tetracycline class antibiotics, and Vitamin A derivatives (including isotretinoin and alltransretinoic acid) [76,77]. Importantly when the drug has been stopped the ICP settles.

6. Management

The principles of IIH management include sight preservation, symptom control and treatment of underlying aetiology [9]. There is a spectrum of mild to severe disease, and it is still not evident at which point in mild disease to consider therapy, and indeed when to escalate to surgical intervention in more severe disease. A further uncertainty is that while the majority of patients are managed medically with less than 8% undergoing surgical interventions [78], do the surgical interventions ameliorate the underlying systemic disease pathophysiology?

6.1 Sight threatening disease

Fulminant IIH describes sight-threatening disease however, there is no evidence-based definition for this. Decision-making is based on clinical consensus which currently recommends surgical treatment where Frisén grade is 3 or more, increased papilloedema on OCT imaging and visual field loss measured by perimetric mean deviation (PMD) is demonstrated [9]. More recently, the characteristics of a single center practice detaild the following characteristics of a fulminant patient (Table 1) [79].

Fulminant IIH is typically managed surgically through emergency CSF diversion or optic nerve sheath fenestration (ONSF), with fewer people having a neurovascular stent [3,78]. All surgical interventions for IIH have not been subject to a RCT, and hence why reporting bias is present in the literature making it challenging to support any intervention over another.

6.2 CSF diversion

Worldwide CSF shunting is still the most commonly performed surgical treatment for IIH [3][80]. It has a failure rate of 43% with a mean revision rate of 2.6 per patient. The overall serious complication rate for CSF diversion procedures reported was 9.4% with infection being the commonest [81]. There are similar one year failure rates for ventriculoperitoneal shunts compared to lumbar peritoneal shunts (41% and 38% respectively) [81,82]. The Birmingham Standardised IIH Protocol demonstrated improved outcomes [83]. It recommended shunt insertion by neurosurgeons with expertise in CSF disorders, implemented a frontal ventriculoperitoneal shunt with adjustable gravitational valve and monitoring device, frameless insertion of the ventricular catheter and laparoscopic insertion of the peritoneal catheter [83]. The revision rate with this technique was 6.5% at 30 days and 11.3% at 33 months follow-up. Early failures were related to surgical technique and were attributed to the challenges arising from cannulating small ventricles and the body habitus typical of the disease [84].

Telemetric ICP monitors are now inserted routinely in many centers when CSF shunts are placed to allow enhanced disease monitoring and shunt adjustment [83]. They can be interrogated in suspected shunt failure or to determine if headaches are due to high or low ICP.

6.3 Optic nerve sheath fenestration (ONSF)

ONSF surgery is used in centres where the surgical expertise exists. It creates an opening in the dura surrounding the optic nerve to allow the CSF to flow into the orbital compartment. It is particularly indicated for asymmetric papilloedema or when visual symptoms predominate. New techniques of an upper lid skin crease approach have been popularised [85-87]. It carries the risk of severe complications such as loss of vision, as well as diplopia and pupillary dysfunction. About one fifth require further surgical interventions [87].

6.4 Neurovascular stenting

Neurovascular stenting has been popularized over the last two decades as the majority of people with active IIH demonstrating dural venous sinus stenosis along the transverse sinussigmoid sinus junction [30,31,32,37]. Dural venous sinus stenting (DVSS) aims to target venous sinus stenosis, removal of the stenosis reduces venous hypertension and subsequently increases CSF absorption [31,32]. A recent review of surgical techniques in IIH reported a 12-month failure rate of 13.1% with re-stenting or supplementary intervention required in 3.4% of cases [81]. Complications occurred in 9.4% of patients with 2.3% classed as major - these included subdural hematoma, subdural with intracerebral hematoma, subdural hematoma with subarachnoid haemorrhage, bilateral cerebellar hematoma, obstructive hydrocephalus, and death. The commonest complication reported is postprocedure headache, which can occur in up to 30% of patients [88]. Comparatively DVSS was superior to CSF diversion in improving visual outcomes, namely papilloedema reduction and visual field improvement, with fewer revisions or failures reported [81,88]. DVSS has also shown success in improving headache and pulsatile tinnitus [89]. Case series are becoming more sophisticated in terms of their reporting outcomes [37]. A number of RCT plan to address the gap in the literature such as Open-UP (NCT02513914), SIMPLE (NCT05707442) and IIH Intervention (ISRCTN57142415).

6.5 Weight management

Weight management in IIH has proven to be an effective long-term therapy as it reduces ICP and improves symptoms [90-92]. Very low calorie diets have shown success in the short term for improving headaches, lowering ICP and restoring vision [93]. Unfortunately, relapse is common with one-third to one-half of weight regained at one year and return to original weight after five years on average [94]. Weight gain has been associated with worsening papilloedema [95]. The IIH Weight Trial compared bariatric surgery to a dietary weight management program and found that bariatric surgery was superior for long-term weight loss and ICP reduction in women with BMI>35kg/m² in a dose-response relationship [91]. Weight loss of 24% total body weight was effective in achieving remission. Roux-en-Y bypass was the superior procedure for rapid, sustained ICP reduction [92]. In the UK bariatric surgery was cost effective and was shown to save £49,500 and add 1.16 qualityadjusted life years as compared to a dietary weight management program [96].

6.6 Carbonic Anhydrase Inhibition

Acetazolamide lowers ICP directly via carbonic anhydrase inhibition in the choroid plexus, thereby reducing CSF secretion [97]. It is the mainstay of pharmacological treatment in IIH, with two RCTs that have evaluated its efficacy [98,99]. The IIH Treatment Trial (IIHTT) compared a lifestyle weight reduction program with acetazolamide versus a life style weight reduction program with placebo in those with mild visual loss. The IIHTT found that the acetazolamide-plus-diet group had a statistically significant improvement in visual field mean deviation with most of the change occurring in the first month of treatment. In the IIHTT high doses of acetazolamide were used (up to 4g), which for nearly half of people with IIH are unable to tolerate [98,100]. Due to the side-effects, it is recommended to titrate up the drug over a few weeks [56]. Side-effects include paraesthesia, dysgeusia, vomiting and diarrhoea, malaise, fatigue, depression and, most seriously, metabolic acidosis [101].

Topiramate is a non-selective carbonic anhydrase inhibitor that is also effective in migraine and has weight-loss properties [102]. It is currently used as an anti-convulsant and has shown efficacy in people with IIH in an open label trial [103]. Some of the side effects including cognitive impairment and depression need to be considered in those with IIH, as it has been shown that cognition is impaired by raised ICP in IIH [50] and anxiety and depression more commonly noted in IIH as compared to the general population [104].

6.7 Headache management

Headache is a near universal symptom of IIH and debate has surrounded the driving mechanisms of headache in this condition [53, 105]. The IIHWT provided evidence that IIH headache is, in part, driven by raised ICP and demonstrated that reduction of ICP reduced headache [106]. In a quantitative metabolomics study acetate was found to be elevated in IIH and is known to stimulate trigeminal sensitization. Also alterations in the urea CSF:serum ratio was noted in people with IIH and was associated with headache pain [106]. It is clear that when ICP is normalized that many continue to suffer from persistent post-IIH headache [11]. The lack of evidence-based management approaches may have led to the increased utilization of preventative migraine therapies and a worrying trend for analgesic prescriptions that were demonstrated in a population controlled epidemiology study [107]. Promisingly a recent prospective open-label study demonstrated the effective use of a

calcitonin gene-related peptide monoclonal antibody therapy in IIH for persistent post-IIH [108]. However, highly effective headache control has been shown to mask disease recurrence, therefore additional ocular monitoring may be required if weight change is noted [109].

6.8 Obstructive Sleep Apnoea (OSA) screening and management

The coexistence of OSA in IIH has been well documented, with both conditions being modified by weight loss [110, 111]. The presence of OSA significantly reduces quality of life and increases the risk of cardiovascular morbidity and mortality [112]. Screening questionnaires such as the STOP-BANG are sensitive screening tool [111]. Overnight pulse oximetry has also been reported as a screening tool with a yield of 48.6% [113].

6.9 Management in pregnancy

The IIH Life maternal health study, which was the largest prospectively collected longitudinal cohort, observed that the majority of people with IIH did not recur during pregnancy and few had escalation of care during the course of their pregnancy [114]. Recent guidance made recommendations for considerations before conception and during pregnancy for those with IIH [115, 116] are summarized at Table 2.

7.0 Future therapeutic avenues

Advances in IIH are focused on employing medical therapies that target the metabolic pathophysiology of raised ICP with two main pathways currently being explored. The role of 11 β -HSD1 in IIH pathophysiology, as described above, has been targeted in a RCT of AZD4017, a 11 β -HSD1 inhibitor [124]. This was a phase 2 RCT and the drug was found to be safe and tolerable, with a high adherence rate (98%). There were no significant differences found in the secondary outcomes of vision or headache disability. Positively, assessment of the metabolic profile associated after AZD4017 treatment showed reduced cholesterol and increased high-density lipoprotein cholesterol [125]. Future studies could consider combining this drug with weight loss methods to determine the synergistic effect with 11 β -HSD1 inhibition.

The other major development for IIH is understanding the glucagon-like peptide-1 (GLP-1) pathway in CSF secretion and ability to modulate this. Exenatide, a (GLP-1) receptor agonist is licensed for treatment of obesity and diabetes mellitus, has also shown ICP-lowering potential in rodent models [126]. The *in vivo* work that identified GLP-1 receptor (GLP-1R) expression in the human and rodent choroid plexus, made the link that an existing drug such as Exenatide could be repurposed for IIH [126]. Physiologically, GLP-1R agonism induces the cAMP-PKA signalling pathway that ultimately inhibits Na+/K+ ATPase in the choroid plexus [51]. Consequently, GLP-1R agonism has been investigated in a RCT with active IIH and using accurate telemetric ICP monitors. This study demonstrated that Exenatide significantly reduced ICP in IIH at 2.5 hours, 24 hours and at 12 weeks, as compared to placebo [127]. An international multi-center trial is currently underway validating GLP-1R agonism in active IIH (NCT05347147).

8.0 Expert Opinion

The increased understanding of the pathophysiology of IIH are having impact with novel targeted therapeutics with 11β -HSD1 and GLP-1R agonism undergoing RCTs. Other technological advances such as optical coherence imaging have made the diagnosis and monitoring of papilloedema easier and are readily accessible world-wide. Telemetric ICP monitoring is providing unique insights to the changes in ICP which previously were unknown and may allow us to correlate the clinical syndrome with changes in ICP [128].

A key area for improvement would be work to understand who would benefit from a medical intervention and who would benefit from a surgical intervention. An area of interest that may develop is a combination of targeting the underlying pathology and need for emergency intervention. The IIHWT observed that ICP was rapidly reduced after bariatric surgery, most prominently with Roux-en-Y gastric bypass (RYBG) surgery, and this appeared to be independent of weight loss as only relatively small changes in body weight had occurred by two weeks [92]. Following a RYBG procedure the bypassed food in the mid/distal jejunum exposes L-cells to nutrients and a sharp rise in GLP-1, oxyntomodulin and peptide YY has been noted. Early improvements in glycaemic control at two weeks post-RYGB in people with type 2 diabetes mellitus were linked to increased post-prandial GLP-1,

oxyntomodulin and peptide YY secretion [129]. Therefore if the reduction in ICP observed at two weeks is potentially driven by GLP-1, two possibilities exist for future exploration. RYGB surgery could be considered earlier in a person's disease course for neuro-ocular and systemic control. Another approach could be to investigate direct GLP-1R agonism in sight threatening disease as the emergency intervention, temporising the disease until systemic treatment was employed.

The past five years has had a high yield for increased knowledge of IIH, and the next five years should concentrate on methods of systemic disease control to change the associated morbidity of the condition. Headache therapy remains an unmet clinical need, and research should focus on this area of high burden for improvement in patient's quality of life [130]. Those professionals that care for people with IIH and those with a lived experience of the condition must continue the dialogue of determining the optimal outcomes for clinical trials that are reliable, disease-specific and acceptable for patients and regulators to continue to advance the field.

Article highlights

IIH is emerging a systemic metabolic disease. Many of the newly recognised disease features are in excess than that driven by the presence of obesity. These include an increased twofold risk of cardiovascular disease, reduced fertility and the pregnancy complications of pre-eclampsia and gestational diabetes.

Adipose tissue in IIH has a unique profile of transcription and metabolic dysregulation driving lipogenesis and promoting increased adipose deposition. There is evidence of increased truncal adiposity, insulin resistance and hyperleptinemia.

The systemic hormonal signature is characterized by hyperandrogenic and systemic glucocorticoid dysregulation.

GLP-1R is expressed in the human choroid plexus. A GLP-1R agonist has been shown to be safe and reduces ICP acutely and up to 12 weeks in a phase 2 RCT.

Bariatric surgery has recently been shown to be superior to a dietary intervention at sustained disease remission out to two years.

Headache remains the most common symptom and an unmet clinical challenge, with open label evidence showing the successful use of calcitonin gene-related peptide monoclonal antibody therapy. This points towards new mechanistic insights to sensitization of the trigeminovascular pathways in IIH headache.

References

- Wang MTM, Bhatti MT, Danesh-Meyer HV. Idiopathic intracranial hypertension: Pathophysiology, diagnosis and management. J Clin Neurosci. 2022 Jan;95:172-179. doi: 10.1016/j.jocn.2021.11.029. Epub 2021 Dec 17. PMID: 34929642.
- Andrews LE, Liu GT, Ko MW. Idiopathic intracranial hypertension and obesity. Horm Res Paediatr. 2014;81(4):217-25. doi: 10.1159/000357730. Epub 2014 Mar 12.
- 3. Mollan SP, Aguiar M, Evison F, Frew E, Sinclair AJ. The expanding burden of idiopathic intracranial hypertension. Eye 2019;33:478–485
- Adderley NJ, Subramanian A, Nirantharakumar K, Yiangou A, Gokhale KM, Mollan SP, Sinclair AJ. Association Between Idiopathic Intracranial Hypertension and Risk of Cardiovascular Diseases in Women in the United Kingdom. JAMA Neurol. 2019 Sep 1;76(9):1088-1098. doi: 10.1001/jamaneurol.2019.1812.

** Big data study signals that women with IIH appeared to be associated with a 2-fold increase in cardiovascular risk.

- Brahma VL, Snow J, Tam V, Ross AG, Tamhankar MA, Shindler KS, Avery RA, Liu GT, Hamedani AG. Socioeconomic and Geographic Disparities in Idiopathic Intracranial Hypertension. Neurology. 2021 Jun 8;96(23):e2854-e2860. doi: 10.1212/WNL.00000000012037. Epub 2021 May 12.
- Rehder D. Idiopathic Intracranial Hypertension: Review of Clinical Syndrome, Imaging Findings, and Treatment. Curr Probl Diagn Radiol. 2020 May-Jun;49(3):205-214. doi: 10.1067/j.cpradiol.2019.02.012.
- Sinclair AJ, Ball AK, Burdon MA, Clarke CE, Stewart PM, Curnow SJ, Rauz S. Exploring the pathogenesis of IIH: an inflammatory perspective. J Neuroimmunol. 2008 Sep 15;201-202:212-20. doi: 10.1016/j.jneuroim.2008.06.029. Epub 2008 Aug 3.
- Friedman DI, Liu GT, Digre KB. Revised diagnostic criteria for the pseudotumor cerebri syndrome in adults and children. Neurology Sep 2013, 81 (13) 1159-1165; DOI: 10.1212/WNL.0b013e3182a55f17
- Mollan SP, Davies B, Silver NC, Shaw S, Mallucci CL, Wakerley BR, Krishnan A, Chavda SV, Ramalingam S, Edwards J, Hemmings K, Williamson M, Burdon MA, Hassan-Smith G, Digre K, Liu GT, Jensen RH, Sinclair AJ. Idiopathic intracranial hypertension: consensus guidelines on management. J Neurol Neurosurg Psychiatry. 2018 Oct;89(10):1088-1100. doi: 10.1136/jnnp-2017-317440. Epub 2018 Jun 14.

- McCluskey G, Doherty-Allan R, McCarron P, Loftus AM, McCarron LV, Mulholland D, McVerry F, McCarron MO: Meta-analysis and systematic review of population-based epidemiological studies in idiopathic intracranial hypertension. *Eur J Neurol* 2018, 25(10):1218-1227
- Thaller, M., Homer, V., Hyder, Y. *et al.* The idiopathic intracranial hypertension prospective cohort study: evaluation of prognostic factors and outcomes. *J Neurol.* 2022. <u>https://doi.org/10.1007/s00415-022-11402-6</u>
- Goudie C, Shah P, McKee J, Foot B, Kousha O, Blaikie A. The incidence of idiopathic intracranial hypertension in Scotland: a SOSU study. Eye (Lond). 2019 Oct;33(10):1570-1576. doi: 10.1038/s41433-019-0450-y. Epub 2019 Apr 30.
- Miah L, Strafford H, Fonferko-Shadrach B, Hollinghurst J, Sawhney IM, Hadjikoutis S, Rees MI, Powell R, Lacey A, Pickrell WO. Incidence, Prevalence and Healthcare Outcomes in Idiopathic Intracranial Hypertension: A Population Study. Neurology. 2021 Jan 20;96(8):e1251–61. doi: 10.1212/WNL.00000000011463. Epub ahead of print.
- Kilgore KP, Lee MS, Leavitt JA, Mokri B, Hodge DO, Frank RD, Chen JJ. Re-evaluating the Incidence of Idiopathic Intracranial Hypertension in an Era of Increasing Obesity. Ophthalmology. 2017 May;124(5):697-700. doi: 10.1016/j.ophtha.2017.01.006. Epub 2017 Feb 7.
- 15. Matthews YY, Dean F, Lim MJ, McLachlan K, Rigby AS, Solanki GA, White CP, Whitehouse WP, Kennedy CR: Pseudotumor cerebri syndrome in childhood: incidence, clinical profile and risk factors in a national prospective population-based cohort study. *Arch Dis Child* 2017, 102(8):715-721.
- Apperley L, Kumar R, Senniappan S. Idiopathic intracranial hypertension in children with obesity. Acta Paediatr. 2022 Jul;111(7):1420-1426. doi: 10.1111/apa.16343. Epub 2022 Mar 27.
- Lyons HS, Mollan SLP, Liu GT, Bowman R, Thaller M, Sinclair AJ, Mollan SP. Different Characteristics of Pre-Pubertal and Post-Pubertal Idiopathic Intracranial Hypertension: A Narrative Review. Neuro-Ophthalmology. 2022. DOI: <u>10.1080/01658107.2022.2153874</u>
- Mollan SP, Ali F, Hassan-Smith G, Botfield H, Friedman DI, Sinclair AJ: Evolving evidence in adult idiopathic intracranial hypertension: pathophysiology and management. J Neurol Neurosurg Psychiatry 2016, 87(9):982-992.

- Alimajstorovic Z, Westgate CSJ, Jensen RH, Eftekhari S, Mitchell J, Vijay V, Seneviratne SY, Mollan SP, Sinclair AJ. Guide to preclinical models used to study the pathophysiology of idiopathic intracranial hypertension. Eye. 2020. 34, 1321–1333. https://doi.org/10.1038/s41433-019-0751-1
- MacAulay N, Keep RF, Zeuthen T. Cerebrospinal fluid production by the choroid plexus: a century of barrier research revisited. Fluids Barriers CNS. 2022 Mar 22;19(1):26. doi: 10.1186/s12987-022-00323-1.

*Comprehensive review detailing recent advances in the understanding of CSF secretion.

- Eide PK, Pripp AH, Ringstad G, Valnes LM. Impaired glymphatic function in idiopathic intracranial hypertension. Brain Commun. 2021 Mar 21;3(2):fcab043. doi: 10.1093/braincomms/fcab043.
- Eide PK, Hansson HA. A New Perspective on the Pathophysiology of Idiopathic Intracranial Hypertension: Role of the Glia-Neuro-Vascular Interface. Front Mol Neurosci. 2022 Jul 12;15:900057. doi: 10.3389/fnmol.2022.900057.
- Tuță S. Cerebral Venous Outflow Implications in Idiopathic Intracranial Hypertension-From Physiopathology to Treatment. Life (Basel). 2022 Jun 8;12(6):854. doi: 10.3390/life12060854.
- 24. Iliff JJ, Wang M, Liao Y, Plogg BA, Peng W, Gundersen GA, Benveniste H, Vates GE, Deane R, Goldman SA, Nagelhus EA, Nedergaard M. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β. Sci Transl Med. 2012 Aug 15;4(147):147ra111. doi: 10.1126/scitranslmed.3003748* Important review outlining the recent advances in the

knowledge of CSF secretion.

25. O'Reilly MW, Westgate CS, Hornby C, Botfield H, Taylor AE, Markey K, Mitchell JL, Scotton WJ, Mollan SP, Yiangou A, Jenkinson C, Gilligan LC, Sherlock M, Gibney J, Tomlinson JW, Lavery GG, Hodson DJ, Arlt W, Sinclair AJ. A unique androgen excess signature in idiopathic intracranial hypertension is linked to cerebrospinal fluid dynamics. JCI Insight. 2019 Mar 21;4(6):e125348. doi: 10.1172/jci.insight.125348.

*Detailed study reports that IIH patients have a unique signature of androgen excess and provide evidence that androgens can modulate CSF secretion via the choroid plexus.

- 26. Botfield HF, Uldall MS, Westgate CSJ, Mitchell JL, Hagen SM, Gonzalez AM, Hodson DJ, Jensen RH, Sinclair AJ: A glucagon-like peptide-1 receptor agonist reduces intracranial pressure in a rat model of hydrocephalus. *Sci Transl Med* 2017, 9(404).
- 27. Stiebel-Kalish, H., Eyal, S. & Steiner, I. The role of aquaporin-1 in idiopathic and druginduced intracranial hypertension. Med. Hypotheses. 2013 81, 1059–1062.
- Uldall, M. et al. Choroid plexus aquaporin 1 and intracranial pressure are increased in obese rats: towards an idiopathic intracranial hypertension model? Int. J. Obes. 2017. 41, 1141–1147
- Eide PK, Hasan-Olive MM, Hansson HA, Enger R. Increased occurrence of pathological mitochondria in astrocytic perivascular endfoot processes and neurons of idiopathic intracranial hypertension. J Neurosci Res. 2021 Feb;99(2):467-480. doi: 10.1002/jnr.24743. Epub 2020 Oct 26.
- Nicholson P, Brinjikji W, Radovanovic I, Hilditch CA, Tsang ACO, Krings T, Mendes Pereira V, Lenck S. Venous sinus stenting for idiopathic intracranial hypertension: a systematic review and meta-analysis. J Neurointerv Surg. 2019 Apr;11(4):380-385. doi: 10.1136/neurintsurg-2018-014172.
- 31. Zhao K, Gu W, Liu C, Kong D, Zheng C, Chen W, Li X, Liang Y, Zhou H. Advances in the Understanding of the Complex Role of Venous Sinus Stenosis in Idiopathic Intracranial Hypertension. J Magn Reson Imaging. 2022 Sep;56(3):645-654. doi: 10.1002/jmri.28177. Epub 2022 Mar 31.
- *Comprehensive review of venous sinus stenosis in IIH.
- 32. 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 Jan 14;12:1-13. doi: 10.2147/EB.S193027.
- 33. Tian Y, Zhang Z, Jing J, Dong K, Mo D, Wang Y. Anatomic Variation of the Lateral Sinus in Patients With Idiopathic Intracranial Hypertension: Delineation With Black-Blood Contrast-Enhanced MRI. Front Neurol. 2021 Nov 25;12:715857. doi: 10.3389/fneur.2021.715857.
- 34. Rohr A, Dörner L, Stingele R, Buhl R, Alfke K, Jansen O. Reversibility of venous sinus obstruction in idiopathic intracranial hypertension. AJNR Am J Neuroradiol. 2007 Apr;28(4):656-9.

- 35. Buell TJ, Raper DMS, Pomeraniec IJ, Ding D, Chen CJ, Taylor DG, Liu KC. Transient resolution of venous sinus stenosis after high-volume lumbar puncture in a patient with idiopathic intracranial hypertension. J Neurosurg. 2018 Jul;129(1):153-156. doi: 10.3171/2017.3.JNS163181. Epub 2017 Aug 25.
- 26. Eshtiaghi A, Zaslavsky K, Nicholson P, Margolin E. Extent of transverse sinus stenosis does not predict visual outcomes in idiopathic intracranial hypertension. Eye (Lond).
 2022 Jul;36(7):1390-1395. doi: 10.1038/s41433-021-01651-6. Epub 2021 Jun 28.
- Khunte M, Chen H, Colasurdo M, Chaturvedi S, Malhotra A, Gandhi D. National Trends of Cerebral Venous Sinus Stenting for the Treatment of Idiopathic Intracranial Hypertension. Neurology. 2023 Mar 29:10.1212/WNL.00000000207245. doi: 10.1212/WNL.000000000207245
- Grech O, Mollan SP, Wakerley BR, Alimajstorovic Z, Lavery GG, Sinclair AJ. Emerging themes in idiopathic intracranial hypertension. J Neurol. 2020 Dec;267(12):3776-3784. doi: 10.1007/s00415-020-10090-4. Epub 2020 Jul 22.
- 39. Westgate CS, Botfield HF, Alimajstorovic Z, Yiangou A, Walsh M, Smith G, Singhal R, Mitchell JL, Grech O, Markey KA, Hebenstreit D, Tennant DA, Tomlinson JW, Mollan SP, Ludwig C, Akerman I, Lavery GG, Sinclair AJ. Systemic and adipocyte transcriptional and metabolic dysregulation in idiopathic intracranial hypertension. JCI Insight. 2021 May 24;6(10):e145346. doi: 10.1172/jci.insight.145346.

**Case control study evaluates IIH adipose tissue and demonstrate an insulin- and leptinresistant phenotype in IIH in excess of that driven by obesity.

- 40. Schiffer L, Arlt W, O'Reilly MW. Understanding the Role of Androgen Action in Female Adipose Tissue. Front Horm Res. 2019; 53:33-49. doi: 10.1159/000494901. Epub 2019 Sep 9.
- 41. O'Reilly MW, Kempegowda P, Walsh M, Taylor AE, Manolopoulos KN, Allwood JW, Semple RK, Hebenstreit D, Dunn WB, Tomlinson JW, Arlt W. AKR1C3-Mediated Adipose Androgen Generation Drives Lipotoxicity in Women With Polycystic Ovary Syndrome. J Clin Endocrinol Metab. 2017 Sep 1;102(9):3327-3339. doi: 10.1210/jc.2017-00947.
- 42. Avisar I, Gaton DD, Dania H, Stiebel-Kalish H. The prevalence of polycystic ovary syndrome in women with idiopathic intracranial hypertension. Scientifica (Cairo). 2012;2012:708042. doi: 10.6064/2012/708042. Epub 2012 Jul 11.

- 43. Thaller M, Adderley NJ, Subramanian A, Mollan SP, Sinclair AJ. Co-morbid Polycystic
 Ovarian Syndrome with Idiopathic Intracranial Hypertension. Neuroophthalmology.
 2023 Jan 10;47(1):49-52. doi: 10.1080/01658107.2022.2162089
- 44. Hornby C, Mollan SP, Mitchell J, Markey KA, Yangou A, Wright BLC, O'Reilly MW, Sinclair AJ. What Do Transgender Patients Teach Us About Idiopathic Intracranial Hypertension? Neuroophthalmology. 2017 May 10;41(6):326-329. doi: 10.1080/01658107.2017.1316744.
- Nayman T, Hébert M, Ospina LH. Idiopathic intracranial hypertension in a pediatric transgender patient. Am J Ophthalmol Case Rep. 2021 Sep 22;24:101208. doi: 10.1016/j.ajoc.2021.101208.
- 46. Alimajstorovic Z, Pascual-Baixauli E, Hawkes CA, Sharrack B, Loughlin AJ, Romero IA, Preston JE: Cerebrospinal fluid dynamics modulation by diet and cytokines in rats. *Fluids and Barriers of the CNS* 2020, 17(1):10
- 47. Sinclair AJ, Walker EA, Burdon MA, van Beek AP, Kema IP, Hughes BA, Murray PI, Nightingale PG, Stewart PM, Rauz S, Tomlinson JW. Cerebrospinal fluid corticosteroid levels and cortisol metabolism in patients with idiopathic intracranial hypertension: a link between 11beta-HSD1 and intracranial pressure regulation? J Clin Endocrinol Metab. 2010 Dec;95(12):5348-56. doi: 10.1210/jc.2010-0729. Epub 2010 Sep 8.
- 48. Markey KA, Uldall M, Botfield H, Cato LD, Miah MA, Hassan-Smith G, Jensen RH, Gonzalez AM, Sinclair AJ. Idiopathic intracranial hypertension, hormones, and 11βhydroxysteroid dehydrogenases. J Pain Res. 2016 Apr 19;9:223-32. doi: 10.2147/JPR.S80824.
- Westgate CSJ, Markey K, Mitchell JL, Yiangou A, Singhal R, Stewart P, Tomlinson JW, Lavery GG, Mollan SP, Sinclair AJ. Increased systemic and adipose 11β-HSD1 activity in idiopathic intracranial hypertension. Eur J Endocrinol. 2022 Jul 4;187(2):323-333. doi: 10.1530/EJE-22-0108.
- Grech O, Clouter A, Mitchell JL, Alimajstorovic Z, Ottridge RS, Yiangou A, Roque M, Tahrani AA, Nicholls M, Taylor AEet al. Cognitive performance in idiopathic intracranial hypertension and relevance of intracranial pressure. *Brain Communications* 2021 3fcab202.

- Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version).
 Cephalalgia. 2013 Jul;33(9):629-808. doi: 10.1177/0333102413485658.
- 52. Mollan SP, Wakerley BR, Alimajstorovic Z, Mitchell J, Ottridge R, Yiangou A, Thaller M, Gupta A, Grech O, Lavery G, Brock K, Sinclair AJ. Intracranial pressure directly predicts headache morbidity in idiopathic intracranial hypertension. J Headache Pain. 2021 Oct 7;22(1):118. doi: 10.1186/s10194-021-01321-8.
- Mollan SP, Hoffmann J, Sinclair AJ. Advances in the understanding of headache in idiopathic intracranial hypertension. Curr Opin Neurol. 2019 Feb;32(1):92-98. doi: 10.1097/WCO.00000000000651.
- Virdee J, Larcombe S, Vijay V, Sinclair AJ, Dayan M, Mollan SP. Reviewing the Recent Developments in Idiopathic Intracranial Hypertension. Ophthalmol Ther. 2020 Dec;9(4):767-781. doi: 10.1007/s40123-020-00296-0. Epub 2020 Sep 9.
- Mollan SP, Virdee JS, Bilton EJ, Thaller M, Krishan A, Sinclair AJ. Headache for ophthalmologists: current advances in headache understanding and management. Eye (Lond). 2021 Jun;35(6):1574-1586. doi: 10.1038/s41433-021-01421-4. Epub 2021 Feb 12.
- 56. Wakerley BR, Mollan SP, Sinclair AJ. Idiopathic intracranial hypertension: Update on diagnosis and management. Clinical Medicine Jul 2020, 20 (4) 384388; DOI: 10.7861/clinmed.2020-0232
- 57. Vijay V, Mollan SP, Mitchell JL, Bilton E, Alimajstorovic Z, Markey KA, Fong A, Walker JK, Lyons HS, Yiangou A, Tsermoulas G, Brock K, Sinclair AJ. Using Optical Coherence Tomography as a Surrogate of Measurements of Intracranial Pressure in Idiopathic Intracranial Hypertension. JAMA Ophthalmol. 2020 Dec 1;138(12):1264-1271. doi: 10.1001/jamaophthalmol.2020.4242.
- 58. Aojula, A., Mollan, S.P., Horsburgh, J. et al. Segmentation error in spectral domain optical coherence tomography measures of the retinal nerve fibre layer thickness in idiopathic intracranial hypertension. BMC Ophthalmol. 2017. 17, 257. https://doi.org/10.1186/s12886-017-0652-7
- 59. Fraser C, Lueck CJ. Optical coherence tomography: a window to the brain? Pract Neurol 2021, 21, 3130321. Doi: 10.1136/practneurol-2020-002824.

- Xie JS, Donaldson L, Margolin E. Papilledema: A review of etiology, pathophysiology, diagnosis, and management. Surv Ophthalmol. 2022 Jul-Aug;67(4):1135-1159. doi: 10.1016/j.survophthal.2021.11.007. Epub 2021 Nov 20.
- 61. Sarrami AH, Bass DI, Rutman AM, Alexxander MD, Aksakal M, Zhu C, Levitt MR, Mossa-Basha M. Idiopathic intracranial hypertension imaging approaches and the implications in patient management. British Journal of Radiology 2022, 95, 1136. doi: https://doi.org/10.1259/bjr.20220136.
- Turay, S., Kabakus, N., Hanci, F., Tunclar, A., & Hizal, M. Cause or consequence: the relationship between cerebral venous thrombosis and idiopathic intracranial hypertension. Neurologist. 2019. 24(5), 155-160. https://doi.org/10.1097/NRL.0000000000242.
- 63. Onder, H., & Kisbet, T. Neuroimaging findings in patients with idiopathic intracranial hypertension and cerebral venous thrombosis, and their association with clinical features. Neurological Research. 2020. 42(2), 141–147. https://doi.org/10.1080/01616412.2019.1710408.
- 64. Bidot, Samuel MD; Saindane, Amit M. MD; Peragallo, Jason H. MD; Bruce, Beau B. MD, PhD; Newman, Nancy J. MD; Biousse, Valérie MD. Brain Imaging in Idiopathic Intracranial Hypertension. Journal of Neuro-Ophthalmology. 2015; 35:4;400-411 doi: 10.1097/WNO.000000000000303
- 65. Skipper NT, Igra MS, Littlewood R, Armitage P, Laud PJ, Mollan SP, Sharrack B, Pepper IM, Batty R, Connolly DJA, Hickman SJ. Do Optic Canal Dimensions Measured on CT Influence the Degree of Papilloedema and Visual Dysfunction in Idiopathic Intracranial Hypertension? Neuroophthalmology. 2018 Jun 26;43(1):3-9. doi: 10.1080/01658107.2018.1483406
- 66. 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 Aug;201(2):412-8. doi: 10.2214/AJR.12.9638.
- 67. Kuzan BN, Ilgın C, Kuzan TY, Dericioğlu V, Kahraman-Koytak P, Uluç K, Çimşit NÇ. Accuracy and reliability of magnetic resonance imaging in the diagnosis of idiopathic intracranial hypertension. Eur J Radiol. 2022 Oct;155:110491. doi: 10.1016/j.ejrad.2022.110491. Epub 2022 Aug 17.

- Prabhat N, Chandel S, Takkar DA, Ahuja C, Singh R, Kathirvel S, Lal V. Sensitivity and specificity of neuroimaging signs in patients with idiopathic intracranial hypertension. Neuroradiol J. 2021 Oct;34(5):421-427. doi: 10.1177/19714009211000623. Epub 2021 Mar 8.
- 69. Aung AB, Chen BS, Wicks J, Bruce BB, Meyer BI, Dattilo M, Kedar S, Saindane A, Newman NJ, Biousse V. Presumptive Idiopathic Intracranial Hypertension Based on Neuroimaging Findings: A Referral Pattern Study. J Neuroophthalmol. 2022 Jul 8. doi: 10.1097/WNO.00000000001660. Epub ahead of print.
- 70. Bateman DE, Wingrove B. Comparison of the Range of Lumbar Cerebrospinal Fluid Pressure in Adults With Normal Cerebrospinal Fluid Pressure and in Idiopathic Intracranial Hypertension. J Neuroophthalmol. 2022 Mar 25. doi: 10.1097/WNO.00000000001578.
- 71. Vosoughi AR, Margolin EA, Micieli JA. Can Lumbar Puncture Be Safely Deferred in Patients With Mild Presumed Idiopathic Intracranial Hypertension? J Neuroophthalmol. 2021 Oct 22. doi: 10.1097/WNO.000000000001411.
- 72. Scotton WJ, Mollan SP, Walters T, Doughty S, Botfield H, Markey K, Yiangou A, Williamson S, Sinclair AJ. Characterising the patient experience of diagnostic lumbar puncture in idiopathic intracranial hypertension: a cross-sectional online survey. BMJ Open. 2018 May 30;8(5):e020445. doi: 10.1136/bmjopen-2017-020445.
- 73. 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(2):245-253. doi:10.1177/0333102418782192
- 74. Kilic K, Korsbæk JJ, Jensen RH, Cvetkovic VV. Diagnosis of idiopathic intracranial hypertension - the importance of excluding secondary causes: A systematic review. Cephalalgia. 2022 May;42(6):524-541. doi: 10.1177/03331024211056580. Epub 2021 Nov 25.
- 75. Mollan S, P, Ball A, K, Sinclair A, J, Madill S, A, Clarke C, E, Jacks A, S, Burdon M, A, Matthews T, D: Idiopathic Intracranial Hypertension Associated with Iron Deficiency Anaemia: A Lesson for Management. Eur Neurol 2009;62:105-108. doi: 10.1159/000222781

- 76. Benzimra, J. D., Simon, S., Sinclair, A. J. & Mollan, S. P. Sight-threatening pseudotumour cerebri associated with excess vitamin A supplementation. Pract. Neurol. 2015. 15, 72 73
- 77. Sodhi A, Sheldon CA, Carleton B, Etminan M. Oral fluoroquinolones and risk of secondary pseudotumor cerebri syndrome: Nested case-control study. Neurology 2017; 22;89:792-795.
- 78. Mollan SP, Mytton J, Tsermoulas G, Sinclair AJ. Idiopathic Intracranial Hypertension: Evaluation of Admissions and Emergency Readmissions through the Hospital Episode Statistic Dataset between 2002–2020. Life. 2021; 11(5):417. <u>https://doi.org/10.3390/life11050417</u>
- 79. Hyder YF, Homer V, Thaller M, Byrne M, Tsermoulas G, Piccus R, Mollan SP, Sinclair AJ. Defining the phenotype and prognosis of people with Idiopathic Intracranial Hypertension after cerebrospinal fluid diversion surgery. Am J Ophthalmol. 2023 Jan 19:S0002-9394(23)00026-0. doi: 10.1016/j.ajo.2023.01.016

*Prospective cohort study details the phenotype of those selected for sight saving surgery in a single neuroscience centre.

- 80. Hamedani AG, Thibault DP, Revere KE, Lee JYK, Grady MS, Willis AW, Liu GT. Trends in the Surgical Treatment of Pseudotumor Cerebri Syndrome in the United States. JAMA Netw Open. 2020 Dec 1;3(12):e2029669. doi: 10.1001/jamanetworkopen.2020.29669
- Kalyvas A, Neromyliotis E, Koutsarnakis C, Komaitis S, Drosos E, Skandalakis GP, Pantazi M, Gobin YP, Stranjalis G, Patsalides A. A systematic review of surgical treatments of idiopathic intracranial hypertension (IIH). Neurosurg Rev. 2021 Apr;44(2):773-792. doi: 10.1007/s10143-020-01288-1. Epub 2020 Apr 25.
- *A comprehensive review of surgical interventions utilised for IIH.
- Kalyvas AV, Hughes M, Koutsarnakis C, Moris D, Liakos F, Sakas DE, Stranjalis G, Fouyas I: Efficacy, complications and cost of surgical interventions for idiopathic intracranial hypertension: a systematic review of the literature. *Acta Neurochir (Wien)* 2017, 159(1):33-49.
- 83. Tsermoulas G, Thant KZ, Byrne ME, Whiting JL, White AM, Sinclair AJ, Mollan SP. The Birmingham Standardized Idiopathic Intracranial Hypertension Shunt Protocol: Technical Note. World Neurosurg. 2022 Sep 9;167:147-151. doi: 10.1016/j.wneu.2022.08.154.
 Epub ahead of print.

- 84. Galloway L, Karia K, White AM, Byrne ME, Sinclair AJ, Mollan SP, Tsermoulas G.
 Cerebrospinal fluid shunting protocol for idiopathic intracranial hypertension for an improved revision rate. J Neurosurg. 2021 Oct 8:1-6. doi: 10.3171/2021.5.JNS21821.
 Epub ahead of print.
- 85. Hagen SM, Wegener M, Toft PB, Fugleholm K, Jensen RH, Hamann S. Unilateral Optic Nerve Sheath Fenestration in Idiopathic Intracranial Hypertension: A 6-Month Follow-Up Study on Visual Outcome and Prognostic Markers. Life (Basel). 2021 Jul 31;11(8):778. doi: 10.3390/life11080778
- 86. Trucchi L, Cohen M, Nahon-Esteve S, Lagier J, Leal C, Almairac F, Chau Y, Sedat J, Bozzolo E, Themelin A, Mondot L, Baillif S, Martel A. Optic nerve sheath fenestration: Current status in France and comparison of 6 different surgical approaches. J Fr Ophtalmol. 2023 Feb;46(2):137-147. doi: 10.1016/j.jfo.2022.07.014
- 87. Jefferis JM, Littlewood RA, Pepper IM, Hickman SJ, Salvi SM. Optic nerve sheath fenestration via a supero-medial eyelid skin crease approach for the treatment of idiopathic intracranial hypertension in a UK population. Eye (Lond). 2021 May;35(5):1418-1426. doi: 10.1038/s41433-020-1024-8
- Asif H, Craven CL, Siddiqui AH, Shah SN, Matloob SA, Thorne L, Robertson F, Watkins LD, Toma AK. Idiopathic intracranial hypertension: 120-day clinical, radiological, and manometric outcomes after stent insertion into the dural venous sinus. J Neurosurg. 2018 Sep;129(3):723-731. doi: 10.3171/2017.4.JNS162871. Epub 2017 Oct 6.
- Nicholson P, Brinjikji W, Radovanovic I, Hilditch CA, Tsang ACO, Krings T, Mendes Pereira V, Lenck S. Venous sinus stenting for idiopathic intracranial hypertension: a systematic review and meta-analysis. J Neurointerv Surg. 2019 Apr;11(4):380-385. doi: 10.1136/neurintsurg-2018-014172. Epub 2018 Aug 30.
- 90. Toscano S, Lo Fermo S, Reggio E, Chisari CG, Patti F, Zappia M. An update on idiopathic intracranial hypertension in adults: a look at pathophysiology, diagnostic approach and management. J Neurol. 2021 Sep;268(9):3249-3268. doi: 10.1007/s00415-020-09943-9. Epub 2020 May 27.
- 91. Mollan SP, Mitchell JL, Ottridge RS, Aguiar M, Yiangou A, Alimajstorovic Z, Cartwright DM, Grech O, Lavery GG, Westgate CSJ, Vijay V, Scotton W, Wakerley BR, Matthews TD, Ansons A, Hickman SJ, Benzimra J, Rick C, Singhal R, Tahrani AA, Brock K, Frew E, Sinclair AJ. Effectiveness of Bariatric Surgery vs Community Weight Management Intervention

for the Treatment of Idiopathic Intracranial Hypertension: A Randomized Clinical Trial. JAMA Neurol. 2021 Jun 1;78(6):678-686. doi: 10.1001/jamaneurol.2021.0659.

** A RCT found bariatric surgery was superior to a dietary intervention in lowering intracranial pressure, that was sustained out to two years.

- 92. Mollan SP, Mitchell JL, Yiangou A, Ottridge RS, Alimajstorovic Z, Cartwright DM, Hickman SJ, Markey KA, Singhal R, Tahrani AA, Frew E, Brock K, Sinclair AJ. Association of Amount of Weight Lost After Bariatric Surgery With Intracranial Pressure in Women With Idiopathic Intracranial Hypertension. Neurology. 2022 Sep 13;99(11):e1090-e1099. doi: 10.1212/WNL.00000000200839. Epub 2022 Jul 5.
- 93. Sinclair, AJ, Burdon, MA, Nightingale, *et al*. Low energy diet and intracranial pressure in women with idiopathic intracranial hypertension: prospective cohort study. BMJ 2010; 341: c2701–c2701.
- 94. 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.
- 95. Thaller M, Tsermoulas G, Sun R, Mollan SP and Sinclair AJ. Negative impact of COVID-19 lockdown on papilloedema and idiopathic intracranial hypertension. Journal of Neurology, Neurosurgery & Psychiatry 2021;92:795-797.
- 96. Elliot L, Frew E, Mollan SP, Mitchell JL, Yiangou A, Alimajstorovic Z, Ottridge RS, Wakerley BR, Thaller M, Grech O, Singhal R, Tahrani AA, Harrison M, Sinclair AJ, Aguiar M. Cost-effectiveness of bariatric surgery versus community weight management to treat obesity-related idiopathic intracranial hypertension: evidence from a single-payer healthcare system. Surg Obes Relat Dis. 2021 Jul;17(7):1310-1316. doi: 10.1016/j.soard.2021.03.020. Epub 2021 Mar 30.
- 97. Barbuskaite D, Oernbo EK, Wardman JH, Toft-Bertelsen TL, Conti E, Andreassen SN, Gerkau NJ, Rose CR, MacAulay N. Acetazolamide modulates intracranial pressure directly by its action on the cerebrospinal fluid secretion apparatus. Fluids Barriers CNS. 2022 Jun 29;19(1):53. doi: 10.1186/s12987-022-00348-6.
- 98. Wall M, McDermott MP, Kieburtz KD, Corbett JJ, Feldon SE, Friedman DI. Effect of acetazolamide on visual function in patients with idiopathic intracranial hypertension

and mild visual loss: the idiopathic intracranial hypertension treatment trial. JAMA. 2014;311:1641-51

- 99. Ball AK, Howman A, Wheatley K, Burdon MA, Matthews T, Jacks AS, Lawden M, Sivaguru A, Furmston A, Howell S, Sharrack B, Davies MB, Sinclair AJ, Clarke CE. A randomised controlled trial of treatment for idiopathic intracranial hypertension. J Neurol. 2011 May;258(5):874-81
- 100. ten Hove MW, Friedman DI, Patel AD, Irrcher I, Wall M, McDermott MP; NORDIC Idiopathic Intracranial Hypertension Study Group. Safety and Tolerability of Acetazolamide in the Idiopathic Intracranial Hypertension Treatment Trial. J Neuroophthalmol. 2016 Mar;36(1):13-9. doi: 10.1097/WNO.000000000000322.
- British National Formulary Acetazolamide.
 https://bnf.nice.org.uk/drug/acetazolamide.html. last accessed 27th September, 2022.
- Hu C, Zhang Y, Tan G. Advances in topiramate as prophylactic treatment for migraine. Brain Behav. 2021 Oct;11(10):e2290. doi: 10.1002/brb3.2290. Epub 2021 Sep 2.
- Celebisoy N, Gökçay F, Sirin H, Akyürekli O. Treatment of idiopathic intracranial hypertension: topiramate vs acetazolamide, an open-label study. Acta Neurol Scand.
 2007 Nov;116(5):322-7. doi: 10.1111/j.1600-0404.2007.00905.x.
- Mollan SP, Subramanian A, Perrins M, Nirantharakumar K, Adderley NJ, Sinclair AJ.
 Depression and anxiety in women with idiopathic intracranial hypertension compared to migraine: A matched controlled cohort study. Headache. 2023 Feb 7. doi: 10.1111/head.14465
- 105. Mollan SP, Spitzer D, Nicholl DJ. Raised intracranial pressure in those presenting with headache. BMJ. 2018 Oct 4;363:k3252. doi: 10.1136/bmj.k3252.
- 106. Grech O, Seneviratne SY, Alimajstorovic Z, Yiangou A, Mitchell JL, Smith TB, Mollan SP, Lavery GG, Ludwig C, Sinclair AJ. Nuclear Magnetic Resonance Spectroscopy Metabolomics in Idiopathic Intracranial Hypertension to Identify Markers of Disease and Headache. Neurology. 2022 Sep 8;99(16):e1702–14. doi:
 - 10.1212/WNL.000000000201007.
- 107. Adderley NJ, Subramanian A, Perrins M, Nirantharakumar K, Mollan SP, Sinclair AJ. Headache, Opiate Use, and Prescribing Trends in Women With Idiopathic Intracranial

Hypertension: A Population-Based Matched Cohort Study. Neurology. 2022 Aug 19;99(18):e1968–78.

** Big data study shows women with IIH are prescribed more opiate and simple analgesics compared to both people with migraine and population controls. Their findings suggest that headaches in IIH may be more refractory to treatment that migraine.

- 108. Yiangou A, Mitchell JL, Fisher C, Edwards J, Vijay V, Alimajstorovic Z, Grech O, Lavery GG, Mollan SP, Sinclair AJ. Erenumab for headaches in idiopathic intracranial hypertension: A prospective open-label evaluation. Headache. 2021 Jan;61(1):157-169.
- 109. Yiangou A, Mitchell JL, Vijay V, Grech O, Bilton E, Lavery GG, Fisher C, Edwards J, Mollan SP, Sinclair AJ. Calcitonin gene related peptide monoclonal antibody treats headache in patients with active idiopathic intracranial hypertension. J Headache Pain. 2020 Sep 25;21(1):116
- Sarkhosh K, Switzer NJ, El-Hadi M, Birch DW, Shi X, Karmali S. The impact of bariatric surgery on obstructive sleep apnea: a systematic review. Obes Surg. 2013 Mar;23(3):414-23. doi: 10.1007/s11695-012-0862-2.
- 111. Yiangou A, Mitchell JL, Nicholls M, Chong YJ, Vijay V, Wakerley BR, Lavery GG, Tahrani AA, Mollan SP, Sinclair AJ. Obstructive sleep apnoea in women with idiopathic intracranial hypertension: a sub-study of the idiopathic intracranial hypertension weight randomised controlled trial (IIH: WT). J Neurol. 2022 Apr;269(4):1945-1956. doi: 10.1007/s00415-021-10700-9. Epub 2021 Aug 22.
- 112. Knauert M, Naik S, Gillespie MB, Kryger M. Clinical consequences and economic costs of untreated obstructive sleep apnea syndrome. World J Otorhinolaryngol Head Neck Surg. 2015 Sep 8;1(1):17-27. doi: 10.1016/j.wjorl.2015.08.001.
- 113. Kok LT, Gnoni V, Muza R, Nesbitt A, Leschziner G, Wong SH. Prevalence and utility of overnight pulse oximetry as a screening tool for obstructive sleep apnoea in newly diagnosed idiopathic intracranial hypertension. Eye (Lond). 2022 Feb 24:1–6. doi: 10.1038/s41433-022-01971-1. Epub ahead of print.
- 114. Thaller M, Homer V, Mollan SP, Sinclair AJ. Disease Course and Long-term Outcomes in Pregnant Women With Idiopathic Intracranial Hypertension: The IIH Prospective Maternal Health Study. Neurology. 2023 Feb 7:10.1212/WNL.000000000206854. doi: 10.1212/WNL.000000000206854

- Thaller M, Wakerley BR, Abbott S, Tahrani AA, Mollan SP, Sinclair AJ. Managing idiopathic intracranial hypertension in pregnancy: practical advice. Pract Neurol. 2022 Aug;22(4):295-300. doi: 10.1136/practneurol-2021-003152. Epub 2022 Apr 21.
- Byth LA, Lust K, Jeffree RL, Paine M, Voldanova L, Craven A-M. Management of idiopathic intracranial hypertension in pregnancy. *Obstetric Medicine*. 2022;15(3):160-167. doi:10.1177/1753495X211021333.
- 117. Falardeau J, Lobb BM, Golden S, Maxfield SD, Tanne E. The use of acetazolamide during pregnancy in intracranial hypertension patients. J Neuroophthalmol. 2013 Mar;33(1):9-12. doi: 10.1097/WNO.0b013e3182594001.
- 118. Weston J, Bromley R, Jackson CF, Adab N, Clayton-Smith J, Greenhalgh J, Hounsome J, McKay AJ, Tudur Smith C, Marson AG. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child. Cochrane Database Syst Rev. 2016 Nov 7;11(11):CD010224. doi: 10.1002/14651858.CD010224.pub2.
- 119. McAuliffe FM, Killeen SL, Jacob CM, Hanson MA, Hadar E, McIntyre HD, Kapur A, Kihara AB, Ma RC, Divakar H, Hod M. Management of prepregnancy, pregnancy, and postpartum obesity from the FIGO Pregnancy and Non-Communicable Diseases Committee: A FIGO (International Federation of Gynecology and Obstetrics) guideline. Int J Gynaecol Obstet. 2020 Sep;151 Suppl 1(Suppl 1):16-36. doi: 10.1002/ijgo.13334.
- 120. Thaller M, Mytton J, Wakerley BR, Mollan SP, Sinclair AJ. Idiopathic intracranial hypertension: Evaluation of births and fertility through the Hospital Episode Statistics dataset. BJOG. 2022 Nov;129(12):2019-2027. doi: 10.1111/1471-0528.17241
- 121. National Institute for Health and Care Excellence . *Weight management before during and after pregnancy*, 2010.
- 122. Chih A, Patel B. Idiopathic intracranial hypertension in pregnancy. Fed Pract. 2015 Nov;32(11):36-40.
- 123. Qureshi A, Virdee J, Tsermoulas G, Sinclair AJ, Mollan SP. Optical coherence tomography confirms shunt malfunction and recurrence of raised intracranial pressure in optic atrophy. Br J Neurosurg. 2022 Apr;36(2):185-191
- 124. Markey K, Mitchell J, Botfield H, Ottridge RS, Matthews T, Krishnan A, Woolley R, Westgate C, Yiangou A, Alimajstorovic Z, Shah P, Rick C, Ives N, Taylor AE, Gilligan LC, Jenkinson C, Arlt W, Scotton W, Fairclough RJ, Singhal R, Stewart PM, Tomlinson JW, Lavery GG, Mollan SP, Sinclair AJ. 11β-Hydroxysteroid dehydrogenase type 1 inhibition in

idiopathic intracranial hypertension: a double-blind randomized controlled trial. Brain Commun. 2020 Jan 10;2(1):fcz050. doi: 10.1093/braincomms/fcz050.

- 125. Hardy RS, Botfield H, Markey K, Mitchell JL, Alimajstorovic Z, Westgate CSJ, Sagmeister M, Fairclough RJ, Ottridge RS, Yiangou A, Storbeck KH, Taylor AE, Gilligan LC, Arlt W, Stewart PM, Tomlinson JW, Mollan SP, Lavery GG, Sinclair AJ. 11βHSD1 Inhibition with AZD4017 Improves Lipid Profiles and Lean Muscle Mass in Idiopathic Intracranial Hypertension. J Clin Endocrinol Metab. 2021 Jan 1;106(1):174-187. doi: 10.1210/clinem/dgaa766.
- 126. Botfield HF, Uldall MS, Westgate CSJ, Mitchell JL, Hagen SM, Gonzalez AM, Hodson DJ, Jensen RH, Sinclair AJ: A glucagon-like peptide-1 receptor agonist reduces intracranial pressure in a rat model of hydrocephalus. *Sci Transl Med* 2017, 9(404).
- 127. Mitchell J, Mollan S, Walker J, et al. A randomised controlled, trial of the GLP-1 receptor agonist exenatide in idiopathic intracranial hypertension. Journal of Neurology, Neurosurgery & Psychiatry 2022;93:A98.

** An RCT assessing the effective of exenatide, a GLP-1R agonist on ICP in women with IIH finds that exentide significantly reduces ICP at 2.5hours, 24 hours and 12 weeks. They utilized highly accurate telemetric ICP monitors.

128. Mitchell JL, Buckham R, Lyons H, Walker JK, Yiangou A, Sassani M, Thaller M, Grech O, Alimajstorovic Z, Julher M, Tsermoulas G, Brock K, Mollan SP, Sinclair AJ. Evaluation of diurnal and postural intracranial pressure employing telemetric monitoring in idiopathic intracranial hypertension. Fluids Barriers CNS. 2022 Nov 1;19(1):85. doi: 10.1186/s12987-022-00384-2.

* A prospective study utilized highly accurate telemetric ICP monitors and found that ICP rises while IIH patients are supine for prolonged periods of time (such as overnight). They also found that bending and Valsalva manoeuvres only increase ICP for less than 4 seconds.

- 129. Behary P, Tharakan G, Alexiadou K, Johnson N, Wewer Albrechtsen NJ, Kenkre J, et al. Combined GLP-1, Oxyntomodulin, and Peptide YY Improves Body Weight and Glycemia in Obesity and Prediabetes/Type 2 Diabetes: A Randomized, Single-Blinded, Placebo-Controlled Study. Diabetes Care. 2019;42(8):1446-53.
- 130. 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 Mar 15;9(3):e026573. doi: 10.1136/bmjopen-2018-026573.