Current and emerging diagnostic and management approaches for idiopathic intracranial hypertension

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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 11β-hydroxysteroid 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 11β-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]. 11β-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, 11β-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 11β-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 11β-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 r^2-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 all-transretinoic 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 sinus-sigmoid 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 post-procedure 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/m^2 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 quality-adjusted 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 11β-HSD1 in IIH pathophysiology, as described above, has been targeted in a RCT of AZD4017, a 11β-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 11β-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.

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