Idiopathic Intracranial Hypertension and Obesity

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Key Words

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Abstract

Idiopathic intracranial hypertension (IIH), also known as primary pseudotumor cerebri syndrome (PTCS), is a condition of unknown etiology which affects primarily overweight, reproductive-aged women and causes increased intracranial pressure (ICP). This review discusses the recently revised diagnostic criteria for PTCS for adults and children. Additionally, the role of obesity in the epidemiology, etiology, and management of IIH as well as the current knowledge of obesity profiles and markers in IIH are reviewed. We also highlight the emerging, unifying theory of the neuroendocrine effects on the mineralocorticoid receptor to explain a possible mechanism for the increased cerebrospinal fluid production and ICP in secondary PTCS.

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Introduction

Idiopathic intracranial hypertension (IIH), also known as primary pseudotumor cerebri syndrome (PTCS) [1], is a disease of unknown etiology that causes increased intracranial pressure (ICP) without any identifiable cause. It tends to affect young, overweight women of reproductive

age, with symptoms of headache, nausea, vomiting, transient vision loss, impaired visual fields, photopsias, diplopia, and eye pain [2]. Other symptoms of IIH include pulse-synchronous tinnitus, and shoulder or arm pain [2, 3]. Ophthalmologic signs of IIH include decreased visual acuity, visual field loss, and papilledema. Permanent vision loss may affect up to 30% of patients [2], and sixth or seventh nerve palsies may also be present [2]. In the pediatric population, the signs and symptoms of IIH can be variable. Children can describe visual symptoms including transient visual loss, photophobia, and ‘shimmering lights with colored centers’ [4]. Headache is the main symptom among children with IIH and it has been documented in 62–91% of cases [5–7]. Of note, for unclear reasons there are reports of IIH without headache symptoms in children, either because the child is too young to articulate or because the headache is truly absent [8–11]. Children with IIH but without the headache tend to have more neurological signs, and vision loss at presentation is associated with a poorer prognosis [6]. Additionally, in pediatric cases of IIH the presentation may mimic a lesion in the posterior fossa with ataxia, facial palsy, nuchal rigidity, and torticollis [12].

This review encompasses the newly revised diagnostic criteria for PTCS in adults and children and the role of obesity in the epidemiology, etiology, and management of IIH. It also covers our current knowledge of obesity profiles and markers in IIH. Other recent reviews, including one on pediatric IIH [13] which we published in *Hormone Re-*

Table 1. Updated 2013 diagnostic criteria for the PTCS [1]

Diagnosis of PTCS	A Papilledema B Benign neurologic exam C Normal CSF composition D Normal neuroimaging without signs of hydrocephalus or mass or parenchymal structural defects and without meningeal enhancement on MRI E Elevated lumbar puncture opening pressure			May have cranial nerve abnormalities MRI +/- contrast MRI +/- contrast with MRV May use contrast CT if MRI is unavailable ≥250 mm H ₂ O ≥280 mm H ₂ O ≥250 mm H ₂ O	Obese females All others Adults Children Children: not sedated or obese
Diagnosis of PTCS without papilledema	1 B to E from the above criteria are satisfied 2 Unilateral or bilateral abducens nerve palsy				
Probable PTCS	1 A to D from the above criteria are satisfied 2 Normal lumbar puncture opening pressure				
Suggested PTCS	1 B to E from the above criteria are satisfied 2 Neuroimaging shows at least 3 of the following: Empty sella Flattening of the posterior globe Distension of the perioptic subarachnoid space +/- tortuous optic nerve Transverse venous sinus stenosis				

search in Paediatrics in 2010, can provide further scope regarding the multifactorial pathophysiology and treatment options of this disease in adults [14, 15] and in children.

Search Strategy

PubMed was utilized to search for IIH and pseudotumor cerebri each with: weight, obesity, pediatric obesity, weight gain, weight loss, gastric bypass surgery, weight loss surgery, aldosterone, and growth hormone. IIH was specifically searched with adiposity, leptin, cortisol, obstructive sleep apnea, economic cost, pathophysiology, diagnostic criteria, and epidemiology. Searches were performed both with a publication date filter of 1995 to the present and without a filter. The reference lists of identified articles were also searched for further relevant articles.

Nomenclature and Diagnostic Criteria

The diagnosis of PTCS was first characterized by Dandy [16] in 1937. The criteria were later modified by Smith [17] in 1985 (modified Dandy criteria), again by Fried-

man and Jacobson [18] in 2002, and most recently by Friedman et al. [1] in 2013 (table 1). New terminology and criteria were necessary to incorporate advances in the knowledge of PTCS over the last decade, including insights of normal opening pressure in children, the characterization of typical neuroimaging abnormalities, and understanding of the features distinguishing intracranial hypertension with and without papilledema. Additionally, due to confusion with numerous terms utilized to describe the disorder, including 'pseudotumor cerebri,' 'idiopathic intracranial hypertension,' and 'benign intracranial hypertension,' the authors of the new criteria felt the condition was best described using the umbrella term 'pseudotumor cerebri syndrome'. This term encompasses both primary (idiopathic) and secondary causes of intracranial hypertension (venous sinus thrombosis, medications, or medical conditions). Based on the new criteria, IIH is considered a subset within primary PTCS.

According to the newly proposed criteria, a 'definitive' diagnosis of PTCS requires: papilledema, a normal neurologic exam other than cranial nerve abnormalities, a normal cerebrospinal fluid (CSF) composition, an elevated lumbar puncture opening pressure (≥280 mm CSF in children or ≥250 mm CSF in adults or unsedated, non-

obese children), and normal neuroimaging. For the neuroimaging, there should be normal brain parenchyma (no evidence of hydrocephalus, mass or structural lesions, or meningeal enhancement) on MRI with and without gadolinium for typical patients (female and obese). For all other types of patients, MRI with and without gadolinium and MR venography should be performed. When MRI is unavailable or contraindicated, contrast-enhanced CT of the head may be used. PTCS is considered 'probable' if the above criteria are met in the presence of an opening pressure lower than specified for a 'definite' diagnosis. The diagnosis can also be made in the absence of papilledema if the patient has all of the above criteria including unilateral or bilateral abducens nerve palsy. In the absence of papilledema or sixth nerve palsy, the diagnosis of PTCS is 'suggested' if all other criteria are satisfied and the patient has at least 3 key findings on neuroimaging (empty sella, flattening of the posterior aspect of the globe, distention of the perioptic subarachnoid space with or without a tortuous optic nerve, or transverse venous sinus stenosis) [1].

PTCS Etiology

While the etiology of IIH remains unknown, there have been many postulated theories. Proposed mechanisms that could explain the elevated ICP in IIH include increased cerebral volume (either interstitial fluid, blood or tissue), increased CSF volume due to increased production or resistance to CSF outflow, loss of cerebral autoregulation resulting in elevated cerebral arterial pressure, or increased cerebral venous pressure leading to increased CSF volume and decreased CSF outflow [19]. Secondary PTCS can be caused by many medical conditions and medication side effects, of which an exhaustive list is detailed in the literature [2, 18]. Notably, disorders of the hypothalamic-pituitary-adrenal axis such as Addison's disease and Cushing's disease, and withdrawal from chronic use of corticosteroids, have been shown to be associated with the development of secondary PTCS [20]. Among medication associations, there are many case reports of secondary PTCS following the use of tetracycline compounds and hypervitaminosis A [2, 18].

A recent study proposed a theory unifying various neuroendocrine effects on the mineralocorticoid receptor (MR) to explain a possible mechanism for the increased CSF production and ICP in secondary PTCS [21]. The MR is abundant in choroid plexus (CP) epithelial cells, which regulate CSF production. Activation of the

MR or its downstream pathways can enhance and stimulate the generation of Na/K ATPase pumps, which can lead to the movement of sodium ions at the CP apical membrane into the cerebral ventricle and actively create an osmotic gradient to drive CSF secretion and increase CSF pressure [21]. The authors hypothesize that this may be a key mechanism for secondary PTCS in patients with hyperaldosteronism, obesity, hypercortisolism, hypervitaminosis A, and recombinant growth hormone. For example, aldosterone, a mineralocorticoid (MC) responsible for Na⁺ resorption and K⁺, Ca²⁺, and Mg²⁺ excretion at target tissues, including the epithelial cells of the CP, can exert its biologic effects on these cells via the MR [21]. An increase in its activity in disorders of primary or secondary hyperaldosteronism may potentially directly affect the ICP in IIH. Support for this hypothesis includes numerous recent studies demonstrating that, in children and adults with primary or secondary hyperaldosteronism, those treated with spironolactone, an aldosterone receptor antagonist, had resolution of symptoms [22]. Additional pediatric cases further strengthen this link of IIH associated with hyperaldosteronism whereby children have been successfully controlled with spironolactone after failure of acetazolamide treatment. In one case the child had secondary hyperaldosteronism, and in the other case the child had metabolic syndrome, obesity, and hyperaldosteronism [12, 23].

The authors also postulate that various reported associations with IIH, including obesity, may all have a unified action on the MR pathway. CSF cortisol levels regulated by 11- β -hydroxysteroid dehydrogenase, an abundant enzyme in the CP which converts inactive cortisone to cortisol, can act with high affinity at the MR in the CP. Thus, derangements of the corticosteroid axis through exogenous or endogenous mechanisms may lead to the development of IIH via this mechanism. Human fat, an active endocrine tissue, secretes MC-releasing factors, providing another possible link for elevated ICP in obese patients with IIH. Vitamin A has been shown to induce expression of neurosteroids in glial cell lines, which could also theoretically interact with MC receptors [21]. Finally, a relationship between IIH and recombinant growth hormone therapy has been reported numerous times and recombinant growth hormone has been regularly associated with increased plasma renin activity and aldosterone levels [21, 24–26]. Thus, this theory proposes that the above mentioned associations with IIH may all have a unified action on the MR pathway in the CP, resulting in altered CSF fluid dynamics and elevated ICP [21].

Table 2. Epidemiologic studies on IIH and obesity

Study location	IIH incidence in the general population		IIH incidence in the overweight/obese population or percent of IIH patients who are overweight/obese	
Iowa, USA [27] ^{2, 4}	0.9/100,000 3.5/100,000	RA ♀	13/100,000 19.3/100,000	Overweight ♀ Obese ♀
Louisiana, USA [27] ^{3, 4}	1.07/100,000		14.85/100,000	Obese ♀
Minnesota, USA [8] ^{1, 4}	0.9/100,000 1.6/100,000 3.3/100,000	♀ RA ♀	7.9/100,000	Overweight
Detroit Medical Center, USA [67] ^{3, 4}	–		90%	Obese
Northern Ireland [28] ⁴	0.5/100,000 0.9/100,000	♀	–	
Parma, Italy [29] ^{1, 4}	0.28/100,000 0.65/100,000	RA ♀	2.7/100,000	Overweight RA ♀
Western Turkey [68] ³	–		30%	Obese
Hokkaido, Japan (2 patients) [31] ¹	0.03/100,000 (2/5,780,000)		–	
Korea (10 patients) [34] ^{1, 4}	–		50% 7.1%	Overweight Obese
China (12 patients) [35] ^{1, 4}	–		33%	Obese
Libya [32] ^{2, 4}	2.2/100,000 4.3/100,000 12/100,000	♀ RA ♀	21.4/100,000	Obese ♀
Israel [30] ^{1, 3}	0.57–0.94/100,000 1.82/100,000 4.02/100,000	♀ RA ♀	97.2%	Obese ♀
Sheffield, UK [33] ¹	1.56/100,000 2.86/100,000	♀	11.9/100,000	Obese ♀

Various methods were used to define overweight and obese. Unless otherwise specified, data includes both men and women of the general population. RA = Reproductive age; ♀ = women.

¹ Overweight: BMI >25 or 26 (variable study parameters); obese: BMI >30.

² Patients >10% over the ideal body weight (overweight) or >20% over the ideal body weight (obese).

³ Obesity based on examiner impression or not specifically defined.

⁴ Study includes patients less than 18 years of age.

Epidemiology and Obesity

Many epidemiological studies have characterized the incidence of IIH and its association with obesity as defined by an elevated body mass index (BMI), although some studies have utilized other methods including the examiner's impression of the patient's weight (table 2). On average, the incidence of IIH in the general population is 0.5–1.0/100,000 [8, 27–30]. The general popula-

tion numbers appear to be lower in some Asian countries [31] and higher in Libya [32] and the UK [33]. Authors of both Italian [29] and UK [33] studies feel that the discrepancies between their IIH and obesity rates and published data could be due to variable obesity rates within their particular populations. The low incidence of IIH in Japan [31], and the lower prevalence of obesity among IIH patients in Korea [34] and China [35], is an interesting finding. Although these studies are quite small, there is some

speculation that obesity does not play as prominent a role in the development of IHH in Asian patients. Kapoor [36], however, cautions that standard definitions of obesity based on the BMI may not necessarily be universally applicable to all races, and that obesity thresholds in Asian populations should perhaps be lower, thus increasing the number of Asian patients with IHH classified as overweight or obese. These trends within the Asian population may warrant further investigation.

Additionally, although there is less epidemiologic data on pediatric IHH, a recent German study found a similar incidence of 0.5/100,000 [37]. The interest in pediatric IHH is increasing due to epidemic childhood obesity rates, with a rate of 16.9% in US children and adolescents in 2009–2010 [38]. Although prior evidence linking pediatric IHH to obesity has been inconclusive, a recent cross-sectional study of 78 children and adolescents with IHH found that 73.1% were overweight or obese, with higher weight classes having progressively higher odds of disease [39]. White non-Hispanic race and female sex in patients older than 11 years were also risk factors. Given this evidence, authors speculate that childhood obesity rates may result in increased morbidity from IHH in this population [39].

Finally, with the striking tendency of IHH to afflict young obese women, a few studies have attempted to further characterize the condition by studying IHH in men. Kesler et al. [40] identified 18 men out of 134 patients with IHH and found that men and women had similar clinical features and outcomes, but far fewer men were overweight or obese (25% of males vs. 77.8% of females). Characterizations of weight, however, were made based on the examiner's impression, not the BMI. Another study also found that men with IHH had more severe vision loss and were less likely to be obese compared to women [41]. Bruce et al. [42], however, reported that in 66 men out of 721 patients with IHH, no difference in BMI was found between men and women, but men were more likely to have obstructive sleep apnea (OSA) (24% of men vs. 4% of women) and twice as likely to suffer serious vision loss. Similarly, another study found that men with IHH were more likely to have OSA than age- and BMI-matched controls, and they also have an increased prevalence of testosterone deficiency symptoms [43]. With conflicting results, it is unclear if obesity factors as greatly in the development of IHH in men compared to women [40–42]. There appears to be a consensus that men with IHH may be at a higher risk for severe vision loss and their management likely requires additional clinical surveillance for vision loss and OSA [41–43].

Weight Gain and Weight Loss

Regarding weight gain, Daniels et al. [44] found that, in 34 newly diagnosed IHH patients and 41 controls, IHH patients reported higher degrees of weight gain in the 12 months prior to the onset of IHH. Higher BMI and percentages of weight gain were also associated with a dose-dependent risk of developing IHH. Interestingly, both previously obese and nonobese patients (BMI <30) had a similar increased risk of developing IHH with only a small weight gain of 5–15% [44]. Other studies have also reported an association between recent weight gain and the onset of IHH [3, 45, 46]. In a case-control study of 50 women with IHH, patients with a recurrence of IHH (26/50) had a higher BMI at recurrence compared to their BMI at diagnosis and at the initial resolution of symptoms [47]. On average, these patients had a 6% weight gain between resolution and recurrence, a finding which is similar to the numbers reported by Daniels [44] and actually corresponds with another study which found that just an average of 6% weight loss resulted in complete resolution of papilledema in IHH patients [48]. Conversely, patients without recurrence had a lower BMI at follow-up compared to diagnosis [47]. Of significance, in this study the average weight of patients without recurrence was greater than that of patients with recurrence throughout the study, suggesting that weight change may be equally important in the development and resolution of IHH compared to baseline weight [47]. Evidence supporting the importance of recent weight gain versus baseline weight also exists in the pediatric population. In a study of 14 pediatric patients with IHH, all 5 patients with excess weight reported the majority of the weight gain within the 18 months prior to developing symptoms of IHH [49]. Despite these results, it is important to note that one third to one half of IHH patients do not exhibit any weight gain prior to the onset of their disease, although these data have often been based on self-reported weight [28, 29, 44]. The studies above suggest that both recent weight gain and baseline BMI are likely critical in IHH pathogenesis and underscore the importance of losing and maintaining weight loss.

Weight loss is also an important predictor of disease progression and visual outcomes. This was originally discussed in 1974 by Newborg [50], who utilized a rice reduction diet for the treatment of IHH. All patients on this low-calorie, low-salt diet had weight reduction and improvement of symptoms. More recently, Burdon et al. [51] followed 25 women with chronic, stable IHH through a 3-stage study, including 3 months each of: no intervention, a 425-kcal diet, and a follow-up period. All women

in the study who lost weight reduced their ICP and demonstrated improvement of papilledema, Pelli-Robson contrast, and Humphrey visual field mean deviations. The headache severity and frequency improved, analgesic use declined, and patients reported fewer symptoms of IIH. Importantly, only 4 of these women reduced their ICP to below 20 cm H₂O, suggesting that patients may not need to reduce their ICP to normal levels to achieve dramatic improvement in the signs and symptoms of IIH [51]. In another retrospective study of 58 women with IIH who were followed for at least 6 months, patients were divided into 2 groups: those who had lost at least 2.5 kg in some 3-month interval during the study and those who had not [52]. Although there was no difference in final visual acuity outcomes between groups, the mean time to improvement of papilledema and visual fields was significantly lower in the weight loss group, again highlighting the importance of weight loss for the disease course. In another small study of 15 obese adult women with IIH treated with only weight loss and/or acetazolamide for 24 weeks, 11 of 15 patients had complete resolution or improvement of papilledema [48]. The amount of weight loss was associated with the degree of improvement of papilledema, and all patients with improvement of papilledema had unchanged normal or improved visual fields. As above [52], it was found that relatively small amounts of weight loss were of great benefit, as the average weight loss of those with complete resolution of papilledema was just 6.2% [48]. As a whole, the data supports the role of weight loss in the treatment of IIH. Although patients may require other treatment modalities, given the benefits of even modest weight loss on IIH disease progression and outcomes, this should be an area of emphasis for treating physicians.

Degree of Obesity and Disease Outcomes

There is still uncertainty as to whether the degree of obesity affects the severity of symptoms and disease outcomes, particular visual field defects. In a new study of 414 IIH patients, those with BMI >40 were more likely to present with severe papilledema and showed a trend of more severe visual loss at follow-up than less obese patients [53]. These authors also reported that for every 10-unit increase in BMI the odds of severe vision loss increased by 1.4 times. In another recent study of 159 female patients with IIH [54], when comparing those with BMI >40 in the year before the diagnosis to those with BMI <40, patients with BMI in the higher group had a higher prevalence of visual

field defects. Another study of 34 patients also showed that severe obesity (BMI >40) was associated with worse visual outcomes [45]. Thus, it appears that those with morbid obesity (BMI >40) have worse visual outcomes and this further underscores the importance of aggressively pursuing weight loss options in extremely obese patients.

Bariatric Surgery and IIH

With weight loss as the cornerstone in treating IIH, the role of weight loss surgery has become an important consideration. Sugerman et al. [55] has provided much of the data on the role of gastric surgery and resolution of IIH. In their 1995 study, 8 patients treated with acetazolamide underwent gastric bypass surgery. Preoperatively, 5 patients continued to have papilledema and all complained of headache with elevated CSF pressure. Following surgery, all patients had resolution of papilledema and lowering of the ICP [55]. These results demonstrated the possible utility of weight loss surgery in the treatment of IIH. Another study of 24 patients with severe obesity found that those who underwent bariatric surgery had a higher success rate for resolution of the symptoms of IIH compared to patients who had CSF peritoneal shunting [56]. Weight loss surgery also provides the additional benefit of resolution of other obesity-related comorbidities such as degenerative joint disease, hypertension, diabetes, and sleep apnea [56]. A review of 11 publications (62 patients) found that 92% of patients with IIH who underwent weight loss surgery had resolution of their symptoms [57]. Of the patients with complete data available, 97% had resolution of papilledema [57]. Additionally, although data on the use of bariatric surgery to successfully treat medically resistant IIH in pediatric patients is lacking, case reports do exist in adolescents. In one case, a 16-year-old obese female with IIH who failed both medical management and shunt placement had resolution of symptoms after bariatric surgery-induced weight loss [58]. Given the rising prevalence of extreme childhood obesity, further research on this treatment is needed. Altogether, the evidence supports the likely utility of weight loss surgery in treating IIH in obese patients, particularly when other strategies have failed.

Adiposity and Obesity Markers

Numerous studies have sought to characterize adiposity and markers of obesity in the setting of IIH, including a comparison by Kesler et al. [59] of 44 female IIH pa-

tients versus 383 obese female patients presenting to an obesity clinic or participating in a national health survey. As the BMI does not address regional fat distribution, this study compared waist-to-hip ratios and waist circumferences and found both were significantly lower in IIH patients versus obesity-matched controls. Pure lower-body adiposity was quite common in the IIH patients (45.4%), but uncommon in the control obese participants (2.1–7.2%) [59]. Another study also found significantly lower waist-to-hip ratios in IIH patients compared to obese controls despite the BMI of the IIH group being an average of 7 points higher [60]. Kesler et al. [59] contend that these results refute an often cited hypothesis of IIH pathogenesis that intra-abdominal fat increases intra-abdominal pressure, resulting in increased intracranial venous pressure [15, 61], since most IIH patients had a higher proportion of lower-body fat versus central obesity. Kesler et al. [59] also propose that the prevalence of an estrogenic gynecoid (pear-shaped) fat distribution and the propensity of IIH to affect obese women in their reproductive years support looking further into the role of estrogen in this disease. Peripheral conversion of androgens to estrogens in adipocytes, elevation of circulating estrogens in the reproductive years, the association of a gynecoid fat distribution with the onset of puberty [59], and reports of the onset of IIH in postmenopausal women following the initiation of hormone replacement therapy [62] lend support to the estrogen theory.

Obesity markers, particularly leptin, possibly contributing to IIH have been extensively examined. Lampl et al. [63] reported significantly higher serum leptin levels in IIH patients compared to obese controls. Ball et al. [60] also reported significantly higher CSF leptin levels in IIH patients compared to obese controls despite not being able to appreciate this finding among serum levels. Other groups also reported positive correlations between BMI and serum leptin levels, but their findings were either similar between IIH and control groups or failed to achieve statistical significance [60, 64, 65]. When Behbehani et al. [66] compared women with IIH to obese controls, there was no association between IIH and serum and CSF leptin levels following adjustments for age and BMI. The lack of multivariate regression analysis, small sample sizes, and variations in methodology in these studies make comparison of these results difficult. Additionally, no significant difference has been found between IIH and control obesity groups in serum insulin levels [60, 65] or ghrelin, a gastric hormone involved in weight regulation [65]. Further research in obesity markers may identify their significance in IIH.

Conclusion

While there has been great progress in our understanding of obesity and IIH since the description by Dandy [16] nearly 80 years ago, there is still much to be learned about the etiology, pathophysiology, and exact role of obesity in IIH, particularly within the pediatric population. The continued modification of the diagnostic criteria for PTCS reflects this progress and will likely help physicians make more a more accurate diagnosis. In the last decade alone, we have learned that there may be a lesser role of obesity in Asians [31, 34–36] and men [40, 41], but men and the morbidly obese may experience more severe vision loss [41, 42, 45, 53, 54]. We continue to see a strong association between IIH and recent weight gain [3, 44, 45] (even modest gains of 6%) [47], but encouragingly the converse appears to be true, as a similar amount of weight loss results in significant improvement [48]. For the morbidly obese IIH patient, bariatric surgery is a likely effective treatment [55–57] when noninvasive strategies have failed. Currently, studies of obesity markers in IIH patients have been inconclusive; however, neuroendocrine interactions on CSF secretion via MR activation is an area of active interest. Looking ahead, publication of the highly anticipated results of the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT), a multicenter, prospective, randomized, placebo-controlled trial will likely further our understanding of IIH and its effective treatment strategies.

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