

REVIEW

Idiopathic Intracranial Hypertension: Epidemiology, Pathophysiology, Clinical Features and Contemporary Management

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KEY WORDS: *idiopathic intracranial hypertension; pseudotumour cerebri*

ABBREVIATIONS

ATECO MRV = auto-triggered elliptic-centric-ordered three-dimensional gadolinium-enhanced magnetic resonance venography
BMI = body mass index
CSF = cerebrospinal fluid
ICP = intracranial pressure
IIH = idiopathic intracranial hypertension
LAGB = laparoscopic adjustable gastric banding
LPS = lumboperitoneal shunting
MRI = magnetic resonance imaging
MRV = magnetic resonance venography
ONSF = optic nerve sheath fenestration
RBP = retinol binding protein
TOV = transient obscurations of vision
VPS = ventriculoperitoneal shunting

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*Manuscript received November 28, 2015;
Revised manuscript accepted March 31,
2016*

Conflict of Interest: none declared

ABSTRACT

Idiopathic intracranial hypertension (IIH) is a syndrome of increased intracranial pressure without evident cause. The exact pathogenesis of IIH remains elusive but it is also plausible that the syndrome represents the common final pathway of several different mechanisms. IIH has an estimated incidence of 1-3 per 100,000 and a predilection for obese women of childbearing age. Presentation involves symptomatology and semiology of elevated intracranial pressure, with headache being the most common symptom. Visual disturbances can be devastating, progressive, and may result in permanent visual loss. Moreover, pulsatile tinnitus is frequently encountered. However, asymptomatic presentations are also not uncommon, with patients diagnosed after routine ophthalmological examination illustrates papilledema. Diagnosis is based upon Friedman's criteria. Absence of hydrocephalus or mass lesion and normal cerebrospinal fluid composition need to be confirmed. Several treatment modalities have been suggested, varying from non-surgical (weight loss, drugs such as acetazolamide, serial lumbar punctures) to interventional and surgical (cerebrospinal fluid diversion procedures, optic nerve sheath fenestration, endovascular venous sinus stenting, or even bariatric surgery). There are very few randomized controlled trials that critically assess these therapies and, consequently, no consensus currently exists on the optimal management of IIH.

INTRODUCTION

Idiopathic intracranial hypertension (IIH) or pseudotumor cerebri, is a syndrome of unknown cause that results in elevated intracranial pressure (ICP). This condition occurs in the absence of hydrocephalus or mass lesion and patients have normal cerebrospinal fluid (CSF) composition. Overall incidence is low (0.9/100,000), however, there is a predilection for obese women of childbearing age, in whom the incidence is nearly 20 times higher.¹ Although the symptoms of IIH are not life-threatening, they can be incapacitating secondary to severe headaches, visual disturbance, and potential progression to blindness.

A syndrome which, in the absence of a mass lesion, was presented with brain tu-

mour-like symptoms, named “meningitis serosa”, was initially reported by Quincke in the 1890s.² Later on, Walter Dandy, one of the most distinguished figures of modern neurosurgery, introduced the surgical treatment of the disease by performing subtemporal decompressions in his patients. He described sporadic and rapid elevations of the craniectomy flaps within a period of minutes,³ hypothesizing a dynamic process (such as changes in the vasomotor vascular bed) underlying the syndrome’s pathophysiology.⁴ The nomenclature of the syndrome was updated in 1989, when Corbett and Thomson⁵ introduced the term “idiopathic intracranial hypertension”, to replace the previously used “pseudotumour cerebri” and “benign intracranial hypertension”, because those terms did not reflect the severity of the condition.

EPIDEMIOLOGY

Idiopathic intracranial hypertension has an annual incidence of 0.9 per 100,000 in the general population, and 3.5 per 100,000 in women aged 15-44 years old. However, in obese women of childbearing age (20-44 years old), who exceed the ideal weight by over 20%, the annual incidence is nearly 20 times higher (19 per 100,000). The mean age at the time of diagnosis is 30 years.¹ More than 90% of patients clinically diagnosed with IIH are women of childbearing age, and over 90% are obese.⁶ One should be cautious when diagnosing IIH in the following categories: non-obese individuals, men, elderly, and very young children. The reason is that IIH’s incidence is low in such patients and alternate causes should be considered. In men diagnosed with IIH, black individuals have the greatest risk of visual loss.⁷ IIH affects children as well. However, the incidence does not differ between genders⁸ and the association with obesity is less robust.⁹ Recent weight gain (within a year prior to diagnosis) has been correlated with IIH onset in both obese and non-obese patients.¹⁰

PATHOGENESIS

“Idiopathic” derives from the Greek words “ἴδιος” (idios), meaning “one’s own” and “πάθος” (pathos), meaning “suffering”. It describes “a disease of its own kind” and is used to denote the unknown or obscure cause of a disease or condition. Consequently, as the term idiopathic indicates, the exact pathogenesis of IIH remains elusive. Any theory, in order to be plausible, should interpret the predilection of the syndrome for obese women of childbearing age, the normal size of the ventricular system, and the association of IIH with systemic diseases and particular medications (e.g. tetracyclines).¹¹

Although several theories have been proposed to explain the pathophysiology of the syndrome, none has adequately done so. Consequently, IIH has been described as the “disease

of theories” because no consensus exists as to its pathogenesis. However, it is plausible that the syndrome represents the common final pathway of several different mechanisms.

A. CEREBROSPINAL FLUID (CSF) ABSORPTION/ PRODUCTION ABNORMALITIES

The “impaired CSF absorption” theory seems to be the most popular. Decreased conductance to CSF outflow has been demonstrated through radioisotope cisternography.¹² The CSF is mainly absorbed through the arachnoid villi of the brain, although spinal arachnoid granulations and extracranial lymphatics have been suggested as possible alternative routes^{13,14} and decreased CSF absorption has been attributed to their disorder.¹⁵ Nevertheless, irrespective of the absorption process, if outflow resistance rises, then the intracranial pressure (ICP) must rise in order to allow CSF to be absorbed.

Overproduction of CSF has also been suggested as the etiology of the syndrome. However, the CSF production rate of IIH patients does not seem to be substantially different from that of asymptomatic control subjects.¹⁶ Moreover, an overproduction of CSF would probably result in hydrocephalus, a condition which by definition is inconsistent with IIH.

B. INTRACRANIAL VENOUS HYPERTENSION AND OBESITY

Intracranial venous hypertension has been suggested both as the initial step and the final pathway of IIH. The first arguments about its etiologic nature in IIH were advanced following direct venous manometry studies demonstrating elevated intracranial venous pressure in IIH patients.¹⁷ Elevated intra-abdominal pressure in an obese patient can induce a cascade of elevated pleural, right atrial (preload), and central venous pressures and finally intracranial venous hypertension and IIH.¹⁸ Furthermore, hypercarbia encountered in sleep apnea, which is a known complication of obesity, can lead to intracranial venous hypertension and IIH via cerebral vasodilation.¹⁹

C. INTRACRANIAL VENOUS HYPERTENSION AND VENOUS SINUS STENOSIS

Venous outflow obstruction (venous sinus stenosis) has been implicated as the cause of intracranial venous hypertension and consequently decreased CSF absorption.²⁰ With the utilization of auto-triggered elliptic-centric-ordered three-dimensional gadolinium-enhanced magnetic resonance venography (ATECO MRV), focal venous sinus stenoses, typically in the transverse or upper sigmoid sinus, have been encountered in 93% of IIH patients.²¹ and are attributed to hypertrophied pachionian granulations in most cases.²²

An alternative hypothesis suggests that venous sinus stenosis is the sequela of the syndrome, namely resulting from transverse sinus compression due to elevated ICP.²³ In support, reduction in transverse sinus pressures after CSF withdrawal by lumbar puncture,²⁴ and resolution of sinus ste-

nosis after cerebrospinal fluid diversion,²⁵ have been shown. Contrariwise, reports with persistent venous sinus stenoses after restoration of normal cerebrospinal fluid pressure have also been published.²⁶

D. VITAMIN A

Vitamin A, retinol binding protein (RBP) and retinol levels have been found to be increased in both cerebrospinal fluid and serum of IIH patients, implicating vitamin A in the pathogenesis of IIH.^{27,28} Theories suggest that either vitamin A enhances the transcription of genes associated with CSF production or absorption, thus causing intracranial hypertension²⁹ or RBP functions as a signalling molecule affecting CSF production/drainage.³⁰

E. CEREBRAL EDEMA

Although cerebral edema constitutes one of the first suggested theories of IIH pathogenesis with pathological findings evidenced in one study,³¹ ensuing studies have rejected this theory.³²⁻³⁴

F. OTHER THEORIES AND ASSOCIATED CONDITIONS

The influence of sex hormones in the pathogenesis of IIH has been postulated due to the predominance of the disease in women and a history of menstrual irregularities in many patients.³⁵ Another hypothesis suggests that microthrombi (not evident on magnetic resonance imaging) may obstruct the CSF outflow in patients with thrombophilia and thus, induce intracranial hypertension leading to IIH.³⁶ IIH has been repeatedly associated with various drugs (such as tetracyclines,³⁷ vitamin A³⁸) and systemic illnesses (such as lupus erythematosus,³⁹ uremia,⁴⁰ hypothyroidism⁴¹).

CLINICAL FEATURES

By definition, presentation involves symptomatology and semiology of elevated intracranial pressure, with headache being the most common symptom. Visual disturbances can be devastating, progressive, and may result in permanent visual loss. Moreover, pulsatile tinnitus is frequently encountered. However, asymptomatic presentations are also not uncommon⁴² with patients diagnosed after routine ophthalmological examination illustrating papilledema.

A. HEADACHE

Idiopathic intracranial hypertension typically presents with headache, which is almost always present in the course of the disease.^{43,44} Headache features are that of a pulsatile in nature, worse in the morning, may awaken the patient, associated with photophobia, and often similar to migraine. Nausea and vomiting may accompany the headache.

B. TRANSIENT OBSCURATIONS OF VISION

Transient obscurations of vision (TOV) are short episodes -usually less than one minute- of monocular or binocular visual loss, constitute the most common visual symptom in IIH and may be attributed to momentary ischemia of the optic nerve head. Positional changes can, usually, trigger such episodes.⁴⁵

C. OCULAR MOTILITY DISORDERS

Diplopia is a common symptom in IIH patients and is, probably, attributed to sixth nerve palsy due to its constriction as it exits Dorello's canal.⁴⁶ However, any other cranial nerve palsy should prompt a search for an alternative diagnosis.

D. TINNITUS

Pulsatile tinnitus in IIH has been attributed to turbulence of cerebrospinal fluid -through which vascular pulsations are being transmitted- through the venous sinus stenoses of IIH patients.²¹ Over half of IIH patients experience pulsatile tinnitus, which is unilateral in most instances.⁴⁵

E. PAPILLEDEMA

Papilledema is the cardinal sign and the presumed etiology of visual loss in IIH. However, pseudopapilledema (such as macular drusen or congenital disc abnormalities) is the main differential diagnosis that one should have in mind. Papilledema is classified using the "Frisen Scale", after performing fundoscopy and assessing the appearance of the optic disc.⁴⁷ Thus, it can be categorized in 5 grades from normal optic disc (grade 0) to severe papilloedema (grade 5).

F. VISUAL FIELDS AND VISUAL ACUITY LOSS

Visual loss may ensue as a consequence of neglected papilledema and is typically progressive. Formal perimetry, automated or Goldmann, is routinely utilized to evaluate visual fields. Nevertheless, automated perimetry generates more consistent and comparable values for future evaluations and thus, has a comparative advantage over Goldmann.⁴⁸ The vast majority of IIH patients experience visual field defects. In particular, the most common by far is the enlargement of the blind spot while arcuate scotomas, nasal defects, and general field constrictions also occur.⁴⁹ On the contrary, visual acuity assessed via corrected Snellen acuity scale, is typically normal except for fulminant and long term syndromes or in the context of a detached retina. A possible explanation is that the papillomacular bundle remains unaffected until papilledema progresses to severe grades.⁴⁹ Hence, visual acuity is a relatively poor method for evaluating visual deterioration in IIH. On the contrary, formal perimetry and fundoscopy constitute critical markers for the progression of the syndrome.

DIAGNOSTIC CRITERIA

Diagnosis is based upon the "modified Dandy criteria",

which were initially presented in 1985 and updated by Friedman (Friedman's criteria) in 2002 (Table 1).⁵⁰ All six criteria must be fulfilled. As such, IIH represents a diagnosis of exclusion.

Taking all of the above into consideration, a meticulous neurological examination, ophthalmological assessment (fundoscopy, visual acuity and fields) together with pertinent brain imaging and lumbar puncture are necessary to make the diagnosis of IIH. In this context, the CSF opening pressure should be above 25 cm of water measured in the lateral decubitus position.⁵¹ However, some argue that there is no explicit cutoff level, and values between 20 and 25 cm of water should be regarded as marginal.⁵²

Magnetic resonance imaging (MRI) should arguably be a routine investigation to rule out hydrocephalus or mass lesion through the diagnostic process of IIH. However, due to the presumed involvement of venous sinus stenosis in the pathogenesis of the disease and the imperative exclusion of venous sinus thrombosis in order to diagnose IIH, magnetic resonance venography (MRV) might be a routine investigation in all patients with suspected IIH. MRI is normal in the vast majority of IIH patients. However, there are some MRI features, which are occasionally encountered. These are: small slit-like ventricles, empty sella due to presumed herniation of pituitary through the sellar diaphragm, enlarged perioptic subarachnoid spaces and flattening of the posterior sclera.⁵³⁻⁵⁶

As previously mentioned, IIH is a diagnosis of exclusion. Consequently, alternative diagnoses must be thoroughly considered. Particularly, absence of hydrocephalus, mass lesion, venous sinus thrombosis, hypertensive encephalopathy, pseudopapilloedema, and finally secondary intracranial hypertension due to drugs and systemic illnesses must be established.

TABLE 1. Friedman's Criteria for the Diagnosis of Idiopathic Intracranial Hypertension (IIH)

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|---|
| I. Symptoms, if present, are only those of generalized intracranial hypertension. |
| II. Signs, if present, are only those of generalized intracranial hypertension or papilledema: Intact neurological exam with the exception of visual disturbances, sixth cranial nerve palsy, and papilledema |
| III. Elevated CSF opening pressure, ventricular or lumbar (in the lateral decubitus position) |
| IV. Normal CSF composition |
| V. Absence of hydrocephalus, mass lesion or venous sinus thrombosis on neuro-imaging |
| VI. No other explanation for the raised CSF pressure |

CSF = cerebrospinal fluid

MANAGEMENT

Due to the loose definition of IIH and the debatable cause of the syndrome, several treatment modalities have been suggested over the years, varying from non-surgical to surgical. Current management options are:

- Conservative: weight loss, drugs (acetazolamide, topiramate, furosemide, octreotide), repeated lumbar punctures.
- Surgical and interventional: CSF diversion procedures (ventriculoperitoneal or lumboperitoneal shunting), optic nerve sheath fenestration (ONSF), venous sinus stenting, and bariatric surgery.

These treatments have two substantial objectives: a) prevention of visual loss and preservation or even improvement of visual function b) alleviation of headache. There are no specific therapeutic recommendations for the treatment of IIH. Generally, IIH patients are treated along the following principles:

- No intervention is needed if symptoms remain minor and visual function is unaffected. However, monitoring for possible visual deterioration, especially visual fields, is crucial.
- Should presumed etiologic factors be present (such as tetracyclines or sleep apnea), they must be tackled.⁵⁷
- Medical treatment (using carbonic anhydrase inhibitors and loop diuretics) is the first step of the management and often suffices, halting the progression of IIH.⁵⁸
- Simultaneous weight reduction should be encouraged (if needed) along with symptomatic headache management.
- In cases of inadequacy of medical treatment or progression to visual deterioration despite treatment, surgical intervention should be considered.

A. CONSERVATIVE MANAGEMENT

Weight loss

The benefits of weight loss in the management of IIH patients have been well known for over 30 years.⁵⁹ Resolution of papilledema can be achieved even through a weight loss of approximately 6%, as suggested by retrospective studies.⁶⁰ Hence, the involvement of a dietician early in the course of the disease should be considered for patients with minimal symptoms and unaffected vision. Surgically induced weight loss will be discussed below.

Drugs

Acetazolamide, a carbonic anhydrase inhibitor, is the most popular medication for the management of IIH. Its effect seems to be multifactorial. Acetazolamide exerts its therapeutic effect by decreasing the secretion of CSF via the reduction of sodium ion transport across the choroid plexus and the cardiac filling pressure (preload) via its diuretic effect.⁶¹ It is postulated that acetazolamide may also acts by altering the taste of foods⁶²⁻⁶⁴ and thus resulting in anorexia.

Topiramate, due to its carbonic anhydrase inhibitory effect⁶⁵ and furosemide, due to its diuretic effect⁶⁶ have also been advocated as a means of reducing CSF pressure in the management of IIH. Corticosteroids, formerly utilized for treatment of IIH have been widely abandoned because their long-term serious side effects (such as weight gain and steroid withdrawal) outweigh the short-term beneficial effects.⁶⁷

Serial high-volume lumbar punctures

Withdrawal of CSF by serial high-volume lumbar puncture has been advocated for the treatment of IIH.⁶⁸ However, serial lumbar punctures are of limited long-term value because their therapeutic effect lasts only for 82 minutes,⁶⁹ as this period of time is needed for CSF pressure to regain its former values.

B. SURGICAL MANAGEMENT

Fulminant presentations with ongoing visual deterioration and medically refractory cases are usually treated with surgery. The surgical indications, as suggested by Corbett and Thompson,⁵ are summarized in Table 2. Dandy advocated subtemporal decompressive surgery to manage IIH in the first place. Long-term satisfactory outcomes are published even in relatively recent series.⁴ Nonetheless, this surgical modality has been widely rejected and excluded from contemporary surgical management of IIH due to serious complications (such as seizures and subdural hematoma) and poor cosmetic result. The surgical procedures used in contemporary management are briefly described below.

CSF diversion procedures

Lumboperitoneal shunt (LPS) and ventriculoperitoneal

TABLE 2. Indications for Surgical Intervention in Idiopathic Intracranial Hypertension (IIH)

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| 1. If fail, intolerant to, or non-compliant with maximal medical therapy |
| 2. New worsening visual field defect or enlargement of previously existing visual field defect |
| 3. Reduced visual acuity not due to macular edema |
| 4. Presence of severe visual loss (20/40 or worse) in one or both eyes at time of initial examination |
| 5. Anticipated hypotension induced by treatment of high blood pressure or renal dialysis |
| 6. Psychosocial reasons, such as patient’s inability to perform visual field studies, non-compliance with medications, an itinerant lifestyle |
| 7. Headache unresponsive to standard headache medications |

shunt (VPS) constitute methods to divert the CSF from the lumbar subarachnoid space and the lateral ventricles of the brain, respectively, into the peritoneum. The techniques involve introducing a silastic catheter between two lumbar vertebrae into the subarachnoid space or through a burrhole in the lateral ventricles of the brain, for LPS and VPS respectively. The shunt is placed under the skin and follows the subcutaneous plane until it reaches the anterior abdominal wall just in front of the rectus abdominis, whereby through a breach in the peritoneum the catheter enters the intraperitoneal cavity.

Over the years, the CSF diversion apparatus has been enhanced through incorporation of an intermediate valve for adjustment of CSF flow. The valves used, can either control pressure differential between the two compartments (differential pressure valves) or regulate flow of CSF (flow-regulated valves), and allow for a relatively balanced release of CSF rather than rapid flow. An anti-siphon mechanism can be added to the CSF kit in order to counterbalance overdrainage/underdrainage due to postural changes (e.g. overdrainage when standing).

Traditionally, CSF diversion procedures are being performed in patients with both headache and visual deterioration. The most probable explanation is that CSF diversion procedures achieve good results in both headache alleviation and visual improvement categories.⁷⁰ Concerning VPS, it is usually difficult to cannulate the small-to-normal ventricles of the brain and the available technological adjuncts, such as neuronavigation, play an important role. Complications of these procedures like catheter obstruction are commonly encountered, and in many cases necessitate shunt revision.⁷¹

Optic nerve sheath fenestration

Optic nerve sheath fenestration (ONSF) was introduced by De Wecker in 1872.⁷² Firstly, the surgeon must gain exposure of the optic nerve sheath, immediately posterior to the globe. The globe therefore must be rotated laterally or medially (depends on the technique). Subsequently, a couple of fenestrations in specific part of the optic nerve sheath are performed, sometimes augmented by excision of a window of dura between these fenestrations. The exact mechanism of action is not known. It is postulated that CSF flow through the dural window or sheaths forms a chronic fistula that prevents transmission of high CSF pressure to the optic-nerve head.⁷³ ONSF seems to be effective in improving visual function and pappiledema. However, it is less effective in alleviating headache. Consequently, it is probably a better choice when the primary symptom is visual deterioration.

Venous sinus stenting

Focal stenosis of the transverse sinus (or upper sigmoid) has been demonstrated in many IIH patients. These stenoses have been implicated as either the causative or contributory cause of increased ICP, and thus focused treatment of the

stenotic sinus with a stent has emerged as a new potential treatment strategy. In particular, some argue that regardless of the role of sinus stenosis in IIH pathogenesis (causative or contributory), elevated prestenotic venous pressure must be restored because, either way it results in a vicious cycle of increasing ICP and worsening stenosis.⁴⁹

Through a Seldinger technique, a catheter is advanced from the common femoral vein to the stenotic area of the transverse (or upper sigmoid) sinus. When the sinus stenosis has been reached, deployment of an attached-to-the-catheter expandable metal stent is being performed, thus enabling venous pressure to return to its normal values.

Transverse sinus stenosis and a specific pressure gradient across the stenosis need to be confirmed in order to proceed to venous sinus stenting. Considerable efficacy in visual, headache, and papilledema improvement has been demonstrated. However, much will depend on the durability of its effects, demonstrated in studies with longer follow-up, because a tendency for restenosis around intravascular stents at other sites has been widely recognized.⁷⁴

Bariatric surgery

Most commonly, gastric bypass and in some cases laparoscopic adjustable gastric banding (LAGB) have been performed to treat IIH in obese patients. In Roux-En-Y gastric bypass procedure the stomach is divided to form a small proximal gastric pouch. The jejunum is typically divided below the ligament of Treitz, and the distal segment is thereafter elevated and surgically joined to the gastric pouch to create the alimentary (Roux) limb. Thus, food is bypassing the rest of the stomach, the duodenum and a part of jejunum.⁷⁵

In laparoscopic adjustable gastric banding (LAGB) procedure, a band device with an inflatable balloon is placed around the gastric cardia, approximately 1 cm below the gastroesophageal junction. This inflatable balloon is connected by tube to a subcutaneous port attached to the rectus sheath. Injection of saline into the port will cause balloon inflation, which subsequently leads to narrowing of the stomach.⁷⁶

Bariatric surgery efficacy in treating IIH has not been studied extensively. However, bariatric surgery offers a range of other beneficial effects in the IIH obese patients. Apart from achieving long-term weight loss, the majority of morbidly obese patients who undergo bariatric surgery experience at least improvement of diabetes, hypertension, hyperlipidemia, and obstructive sleep apnea.⁷⁶ Of note, achieving significant weight loss in obese patients with IIH occurs gradually. Consequently, bariatric surgery is not appropriate for fulminant IIH cases or cases with progressive visual loss.⁷⁷

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