

## REVIEW

# What is new about idiopathic intracranial hypertension? An updated review of mechanism and treatment

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## Cephalalgia

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Idiopathic intracranial hypertension (IIH) is the syndrome of raised intracranial pressure without clinical, laboratory or radiological evidence of intracranial pathology. IIH is a relatively rare disease but rapidly increasing incidence is reported due to a global increasing incidence of obesity. Disease course is generally said to be self-limiting within a few months. However, some patients experience a disabling condition of chronic severe headache and visual disturbances for years that limit their capacity to work. Permanent visual defects are serious and not infrequent complications. The pathophysiology of IIH is still not fully understood. Advances in neuroimaging techniques have facilitated the exclusion of associated conditions that may mimic IIH. No causal treatment is yet known for IIH and existing treatment is symptomatic and rarely sufficient. The aim of this review is to provide an updated overview of this potentially disabling disease which may show a future escalating incidence due to obesity. Theories of pathogenesis, diagnostic criteria and treatment strategies are discussed. □ *IIH, review, pathology, diagnosis, treatment*

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### Introduction

Idiopathic intracranial hypertension (IIH), previously termed pseudotumour cerebri (PTC) and benign intracranial hypertension (BIH), is a condition of increased intracranial pressure (ICP) without clinical, laboratory or radiological evidence of intracranial pathology. The typical patient is an obese but otherwise healthy woman of childbearing age with symptoms of increased ICP, i.e. headache, pulsatile tinnitus, transitory visual obscurations and diplopia. Permanent visual defects are serious complications to IIH. The pathophysiology of IIH is still not fully understood, hence no real causal treatment exists. The treatment is symptomatic, either medical or surgical, mostly focusing on normalization of ICP. Both types of treatment are often insufficient and

complicated by side-effects. It is the purpose of this review to provide an updated overview of this potentially disabling disease, its diagnosis and treatment.

### Definition

IIH, the syndrome of increased ICP of unknown aetiology, is a diagnosis of exclusion. The original criteria were formulated in 1937 by Walter Dandy (Dandy Criteria) (1), who described the presence of increased ICP, normal cerebrospinal fluid (CSF) findings and no sign of a brain tumour on ventriculography. It is possible, and even likely that IIH encompasses a number of different conditions with similar phenotype, as judged by our current diagnostic techniques. Certainly some conditions that

formerly fitted into the diagnosis of IIH, such as intracranial venous thrombosis, have now been excluded and established as an individual diagnosis (2). Thus, today's classification describes a more restricted group of patients than before. The criteria as currently formulated in the International Headache Society's (IHS) classification of headache disorders (2nd edition) (3) are outlined in Table 1.

No clear requirements are given for the degree of obesity or choice of neuroimaging investigation. Therefore, in practice, classification of IIH is still ambiguous in routine patient management and research, and the interpretation and comparison of various research results continue to be problematic.

## Epidemiology

IIH is a relatively common disease with an annual incidence of one to two diagnosed cases per 100 000 in the general population, but due to the diagnostic variations discussed above the precise incidence and prevalence are unknown (4–7). The syndrome is seen in all ages but more frequently in obese women in the childbearing age, in which an annual incidence of up to 21 : 100 000 has been reported (4–7). In US studies, approximately 70% of the females are obese (body mass index >26) (4, 5), compared with 36% of women in the general US population within the corresponding time period (5).

Men are less frequently affected. The female:male ratio is 4.3 : 1 to 15 : 1 (4–7). In prepubertal children with IIH no female predominance exists (8, 9). The association with obesity has not been proven in men and prepubertal children (8–10). Familial occurrence

has been encountered in few cases (11–13) but has never been further evaluated.

## Aetiology

The name IIH indicates a condition with unknown aetiology. Over the years a multitude of IIH cases and coinciding conditions and medications have been reported (Table 2), many of which may have arisen by chance.

Subsequent improvement after withdrawal of the medication or treatment of the underlying condition has led to postulations of causal relationships (37–39, 41–43, 56) but these remain unproven. This subgroup of patients is now often claimed to constitute a group of conditions with increased ICP of secondary causes and thus falling outside the classification of the 'true' IIH. Several studies have sought to evaluate the existence of these proposed associations but apart from obesity no convincing evidence exists so far (4, 74–79). Considerable heterogeneity of relatively few patients and ambiguous criteria of classification may explain the negative findings. All cases with a known aetiology should be classified as secondary intracranial hypertension. Larger prospective studies of well-classified patients are required for these associations to be evaluated with sufficient statistical power.

## Pathogenesis

The pathogenesis of IIH remains unknown and IIH may not be a syndrome with a single causative factor. A disorder of mass homeostasis is implicit in

**Table 1** International Headache Society's classification (2nd edition) (3) of idiopathic intracranial hypertension

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1. Alert patient with neurological examination that either is normal or demonstrates any of the following abnormalities:
    - (a) Papilloedema
    - (b) Enlarged blind spot
    - (c) Visual field defect
    - (d) Sixth nerve palsy
  2. Increased CSF pressure (>200 mmH<sub>2</sub>O in the non-obese, >250 mmH<sub>2</sub>O in the obese) measured by lumbar puncture in the recumbent position or by epidural or intraventricular pressure monitoring.
  3. Normal CSF chemistry (low CSF protein is acceptable) and cellularity.
  4. Intracranial disease (including venous sinus thrombosis) ruled out by appropriate investigation.
  5. No metabolic, toxic or hormonal cause of intracranial hypertension.

A presenting headache is attributed to idiopathic intracranial hypertension when the headache develops in close temporal relation to the increased intracranial pressure and improves after withdrawal of CSF. The headache should be progressive with at least one of the following:

- (a) Daily occurrence
  - (b) Diffuse and/or constant non-pulsating pain
  - (c) Aggravated by coughing or straining
-

**Table 2** Proposed aetiological factors of idiopathic intracranial hypertension

Exogene factors	Endogene factors
Tetracyclines (14–20)	<i>Endocrinology</i>
Nitrofurantoin (21)	Irregular menstruation (47, 48)
Nalidixic acid (22)	Pregnancy (49)
Sulfamethoxazole (23)	Oral contraceptives (47, 49)
Penicillin (24)	Turner (50)
Corticosteroid treatment and withdrawal (25–27)	Adrenal insufficiency (51, 52)
NSAID in Bartter's syndrome (28, 29)	Hyperthyroidism (53)
Mesalamine (30)	Hypothyroidism (54)
Lithium carbonate (31, 32)	Hyperaldosteronism (55)
Amiodarone (33, 34)	<i>Haematology</i>
Chlordecon (35)	Anaemia (56–60)
Ciclosporine (36)	Hypercoagulability (61–67)
Vitamin A (37–40)	<i>Others</i>
rhGH and IGF-1 (41–46)	Systemic lupus erythematosus (68)
	Behçet's disease (69)
	Sleep apnoea (70–72)
	Acute respiratory insufficiency (73)

any kind of intracranial hypertension. In theory, IIH may be attributed to the following factors:

- 1 Parenchymal oedema
- 2 Increased cerebral blood volume
- 3 Excessive CSF production
- 4 Compromised CSF resorption
- 5 Venous outflow obstruction

#### *Parenchymal oedema*

Patients with IIH have traditionally been said to have slit-like ventricles (1), indicating an increase in cerebral volume. However, whereas reduction in size of the ventricular system has been reported in some computed tomographic (CT) studies (80–82), others have found normal size of the ventricles (83–86). Indirect evidence of brain oedema has previously been provided by magnetic resonance (MR) studies showing increased water content (87) and water diffusion in subcortical white matter (88). A recent study using more refined MR techniques was not able to reproduce these findings (89).

#### *Increased cerebral blood volume*

Two groups, Raichle *et al.* (90) and Mathew *et al.* (91), reported increased cerebral blood volume (CBV) in IIH, using intracarotid tracer injection, but these patients were anaesthetized. No significant differences in regional CBV in IIH compared with normal subjects were found in a subsequent study of Brooks *et al.* using positron emission tomography (92).

#### *Excessive CSF production*

In a condition with overproduction of CSF, one would expect an increase in ventricular size caused by the increased pressure gradient between the ventricles and the subarachnoid space (93). This relation has been demonstrated in animal studies during intraventricular infusion (94). The normal or decreased ventricular size found in IIH patients suggests that they do not have an increased CSF production. This conclusion is corroborated by demonstration of normal CSF flow values through the cerebral aqueduct in patients with IIH, using velocity-sensitive MR techniques (95).

#### *Compromised CSF resorption*

It is tempting to speculate that IIH could be caused by a CSF resorption defect (96–99) since this would result in increased ICP, with a normal or decreased size of the ventricular system. Studies have demonstrated an abnormally increased outflow resistance in 75–100% of IIH patients (95–97, 100). Interestingly, Guillain-Barré syndrome or spinal tumours with a high CSF protein concentration can present with intracranial hypertension without development of ventriculomegaly (101, 102).

Meningitis, as well as subarachnoid haemorrhage, are also known to present with impaired CSF resorption and raised ICP (103–105), but unlike IIH, these syndromes are commonly accompanied by hydrocephalus. However, in these cases CSF flow

obstruction may also occur at a more proximal level, i.e. in the basal arachnoid membranes, thus causing an obstructive hydrocephalic state.

#### *Venous outflow obstruction*

The association of venous sinus hypertension with some reported cases of IIH, due either to structural factors, i.e. unrecognized sinus thrombosis and extraluminal compression, or to functional factors like arteriovenous malformation and central venous hypertension, has long been recognized. The mechanism by which venous sinus hypertension causes raised CSF pressure is thought to be the increase in resistance of CSF absorption due to an insufficiently high driving pressure gradient from the subarachnoidal space to the venous system. Karahalios et al. (106) has gone so far as to propose venous sinus hypertension to be the final common pathway in many different aetiologies of IIH, but firm evidence is still lacking.

Several reports exist of relationships between intracranial hypertension and thrombosis of the transverse sinus secondary to middle ear disease (107) and head injury (108). In general, more than one-third of patients with cerebral venous thrombosis present with symptoms of intracranial hypertension as the only manifesting sign of venous sinus disease (109). CT scans are normal in half of these subjects (109) and even conventional MRI and eventually MR venography may fail to visualize venous sinus thrombosis (110, 111). Some groups have demonstrated this diagnostic problem by direct retrograde cerebral venography and manometry recordings of sinus pressures (111–113). Especially unrecognized non-occlusive transverse sinus obstruction seems to be more common in IIH than is currently appreciated (111–114).

A predisposition to venous thrombosis is reported to be more frequent in IIH than in the general population. Sussman et al. reported the presence of antiphospholipid antibodies in 29% of 38 patients with IIH (63) compared with 2% in healthy individuals (115). Presence of anticardiolipin antibodies in IIH was reported in 43% of 14 patients by Leker et al. (61) and in 8% of 37 patients by Kesler et al. (66). Yet, the high incidence of antiphospholipid antibodies could represent an epiphenomenon, in which they result from an autoimmune response to exposure of neoepitopes on proteins bound to cell membrane phospholipids, after some kind of cell injury related to IIH (116). Other prothrombotic states, i.e. systemic lupus erythematosus (68), Behçet's disease (69), factor V Leiden deficiency (64), antithrombin III defi-

ciency (63), hyperfibrinogenaemia (63) and hormone therapy (62) in association with IIH have been described but associations may have arisen by chance. Recently, the first study of a genetic polymorphism related to an increased risk of IIH was presented (67). The prevalence of three different factor V polymorphisms was found to be significantly higher in IIH compared with healthy controls. The incidence of acquired prothrombotic factors such as obesity, oral contraceptive intake, pregnancy and infection was also high. An interaction between both genetic and acquired risk factors, consistent with the multifactorial nature of venous thrombosis, was therefore suggested. Similar suggestions were made by Glueck et al. (62), who reported a significantly higher appearance of polycystic ovarian syndrome, lupus anticoagulant, activated partial thromboplastin time and factor VIII. Theories are interesting in connection with the findings of venous sinus outflow obstruction. Thrombosis in the arachnoid granulations has also been suggested to contribute to the pathogenesis of IIH, but evidence for this hypothesis is scarce (68).

The venous outflow obstructions observed in manometry studies might indicate that non-occlusive venous sinus thrombosis is the mechanism of IIH, although other interpretations are possible. King et al. proposed that the sinus hypertension is due to compression of the transverse sinuses by an elevated intracranial pressure. Initially, the dural walls may resist the pressure, but during time the walls become stretched, thus compromising venous outflow, and further increase the intracranial pressure (113). They described eight patients in whom the steep pressure gradient along the transverse sinus fell immediately after drainage of CSF and concluded this was caused by the relief of external dural compression. If the obstruction to venous outflow at the level of the transverse sinus is a secondary effect of the elevated intracranial pressure, the primary cause of IIH continues to be an unsolved puzzle.

Venous sinus hypertension may occasionally be caused by elevated central venous pressure (CVP) (106). Although right heart failure is not a common feature of patients with IIH, central obesity correlates directly to elevated CVP and thus a secondary raised sinus pressure (117–119). A study by Sugeran et al. (120) noted that 19 severely obese IIH patients who underwent bariatric gastric surgery lost an average of  $45 \pm 12$  kg within 1 year. All but one had resolution of headache and pulsatile tinnitus within 4 months of the procedure. Another study of diet-induced weight loss of  $\geq 2.5$  kg within

a 3-month period has been found to be associated with more rapid recovery of papilloedema in patients with IIH compared with those who did not lose weight (121). Although not explaining the characteristic demographic distribution of especially young women with IIH, obesity is traditionally thought to have a causative but yet unknown role in IIH. Alternatively, obesity may be the aggravating factor in a critical high sinus pressure secondary to another pathology. Irrespective of the role in pathogenesis, weight loss in obese IIH subjects is generally advocated as an adjunctive mode of therapy (120, 121).

## Symptoms

Symptoms and signs of IIH should be attributable to raised CSF pressure. Common symptoms are headache, pulsatile tinnitus, nausea, transitory visual obscurations, diplopia and blurred vision. The presenting symptom is often headache, although other symptoms including asymptomatic papilloedema are also seen (Table 3).

The headache has an episodic onset and usually, but not always, develops over weeks to a daily pain of moderate intensity typically aggravating in the morning and during physical activity, the Valsalva manoeuvre and postural changes. Acute onset and more severe cases are also reported (18, 123, 125, 126). The quality and location of the headache seem to be rather uncharacteristic but may resemble a fairly severe chronic migraine associated with daily visual non-aura symptoms. Holocranial as well as

hemicranial, retrobulbar, temporal or occipital locations are described. The pain quality is also variable, being pulsatile, pressing or alternating. Nausea is an accompanying symptom in 20–40%, vomiting is less common (18, 123, 125, 126). No data concerning photo- or phonophobia are available. An existing migraine may be aggravated (127) while the prevalence of a prior history of primary headaches is unknown.

Monocular or binocular transitory visual obscurations (TVO) varying from slight blurring to total loss of light perception are seen in up to 72% of the patients (125). The episodes, lasting less than a minute, may arise several times a day and are provoked by postural changes and the Valsalva manoeuvre. TVOs are usually related to papilloedema but cannot predict the patients at risk of developing permanent visual defects (123). Even though not unique to IIH, TVO are an important symptom since they do not exist in primary headaches. Photopsia and continuous blurring of vision with normal visual acuity are other frequent visual complaints (125, 126).

Sixth nerve palsy with horizontal diplopia serves as a false localizing sign of raised CSF pressure in 20–47% of the patients (18, 126). Although cases of ocular motility disturbances other than sixth nerve palsies have been described in patients with normal CT scans (128–130), they are rare and should raise suspicion of a symptomatic aetiology other than elevated CSF pressure.

Pulsatile bruit-like tinnitus, either unilateral or bilateral, exists in 8–60% of patients (18, 122, 125, 131) with frequency and duration being highly individual (125). Pulsatile tinnitus is reversible and usually resolves whenever CSF pressure normalizes. Turbulence, created when blood flows from the hypertensive intracranial space into the low pressure of the jugular vein, is proposed as the mechanism producing the tinnitus (132). Other symptoms less commonly reported in IIH are episodic paraesthesias in hands and feet (131), radiculopathy (133), neck stiffness (131) and arthralgias (133) suggesting nerve root irritation related to raised CSF pressure. Facial nerve palsies (134, 135) and orthostatic transitory dizziness (131) are also described. Lack of concentration and memory difficulties either primary related to the condition or secondary to the psychological aspects of chronic pain and fear of visual loss are frequent (136–138).

Asymptomatic cases of IIH with papilloedema found during routine ophthalmic examination have also been reported (139), but the incidence and clinical course are uncertain.

**Table 3** Presenting symptoms in idiopathic intracranial hypertension

	(Johnston et al. 122)	(Rush et al. 123)	(Corbett 124)
Patients (no.)	62	63	57
Symptom (%)			
Headache	95	75	81
Diplopia	31	35	33
Visual blurring	65	68	–
TVO	–	46	72
Other	–	22	32
Nausea and vomiting	24	21	?
Dizziness	11	?	?
Tinnitus	11	?	?
Asymptomatic	0	5	?
Other	15	19	?

TVO, Transitory visual obscurations.

## Examination

### *Visual examination*

Papilloedema, the typical sign of intracranial hypertension, is usually bilateral. The presentation can be highly asymmetric or even lacking in one or both eyes (140, 141). Differentiating between pseudopapilloedema, i.e. optic disc drusen and elevated disc in the small hyperoptic eye, and true papilloedema can be a challenge and may require evaluation by a trained neuro-ophthalmologist. The features of papilloedema are blurring of the disc border, absent spontaneous venous pulsation, distended retinal veins and eventually protrusion of the optic disc, peripapillary haemorrhages and exudates or even nerve fibre layer infarcts. In chronic courses of intracranial hypertension, a more greyish appearance of the optic disc may develop due to nerve fibre atrophy.

Features of papilloedema arise when the optic nerve is subjected to a raised perineural pressure causing stasis of the retinal veins and the axoplasmic transportation. The highly individual manifestation of the optic disc may be due to anatomical variations of the optic nerve sheath within which the elevated CSF pressure is transplanted. Presence of an extensive trabecular meshwork within the nerve sheath (141) or a nerve sheath defect might cause a local pressure reduction and thus an asymmetric or missing oedema.

Early papilloedema is usually associated with normal Snellen visual acuity, although subjective complaints of blurred vision may be present. However, acuity may deteriorate rapidly in severe cases of IIH (123, 125, 126, 142). The risk of visual acuity impairment increases with duration of the oedema (124). Causes of loss of visual acuity include nerve fibre atrophy, choroidal folds, macula oedema or exudates, nerve disc infarct or subretinal peripapillary haemorrhages extending to the macula.

Visual field defects appear in up to 96% of patients during the course of IIH (125, 143). Enlargement of the blind spot is frequent and is found in virtually all patients with papilloedema (124, 142, 143). The defect is asymptomatic and usually resolves when the oedema resolves. A gross enlargement may develop when choroidal folds are present. If these folds persist after the papilloedema has disappeared, the enlarged blind spot may persist (144).

Apart from an enlarged blind spot, the types of field defects in IIH are similar to those in glaucoma. Nasal defects, arcuate scotomas and concentric constrictions are the most typical defects. The damage

is localized to the nerve fibre bundles when they enter the oedematous optic disc (143). When defects are small the visual loss is often asymptomatic. At the time when the patient becomes aware of a visual problem, the extent of defect has evolved and the risk of disabling loss of visual function is increased. The speed with which defects occur seems to be individual and they may happen both early and late during the course of disease (123).

Contrast sensitivity may also be affected in IIH. However, this parameter is less sensitive in detecting visual loss and occurs in 25% of patients with IIH compared with the presence of visual field defects in 94% patients (143). Therefore, routine follow-up of patients with IIH should consist of visual acuity testing combined with visual field examination in order to detect progressing deterioration of visual function. Other visual signs of intracranial hypertension are presence of colour vision defects and afferent pupillary defect, but these are highly insensitive tests (124, 125).

### *CSF pressure*

Conventionally, the upper limit of normal CSF opening pressure is defined as 200 mmH<sub>2</sub>O measured with the patient in lateral decubitus position with legs extended and as relaxed as possible. Corbett and Metha have reported pressures between 200 and 250 mmH<sub>2</sub>O in both obese (25%) and non-obese (7%) healthy individuals (145). Bono et al. later failed to reproduce these results (146). Yet, pressure interval between 200 and 250 may be a non-diagnostic grey zone.

Because of the natural fluctuations of ICP in IIH, measuring opening pressure does not always give the true steady-state pressure in otherwise appropriate clinical settings (99). In patients with intracranial hypertension, including IIH, abnormal ICP waveforms are present. Although an elevated steady-state ICP has been reported in up to 93% of IIH patients (100), many patients show long periods of low, or indeed normal, ICP between short periods of marked intracranial hypertension (99). There seems to exist a small group of IIH patients in whom mean pressure is normal and only occasionally dominated by pathological elevations (99, 100, 147). Intermittent increases in ICP may be missed by a single-spot lumbar measurement. Repeated lumbar puncture after a prior normal pressure may be necessary if clinical symptoms clearly suggest increased ICP. Pressure monitoring for several hours through a lumbar drain or an intracranial transducer is recommended (2, 148).

## Neuroimaging

A thorough radiological search to exclude secondary causes of intracranial hypertension is required since brain imaging in IIH according to the definition is normal. CT scan discloses most space-occupying mass lesions, although it is less sensitive than MRI. In particular, venous sinus thrombosis can be difficult to detect (109, 149). In subjects with features of IIH and normal findings by conventional CT scans, venous sinus obstructions are revealed by MRV or conventional angiography in 26–36% of cases (150, 151). The role of CT venography in detecting cerebral vein thrombosis is not yet defined. Even conventional MRI can be misleading (149). Thrombotic material only appears strongly hyperintense the first month (149). Chronic thromboses or partially recanalized thromboses are less obvious on MRI but may be recognizable on MRV, usually showing extensive areas of narrowing or flow gaps (149).

Unfortunately, sensitivity as well as specificity of MRV in detecting transverse sinus outflow obstructions may still be insufficiently high (111, 112, 152, 153). The extent of false-negative and false-positive findings in IIH patients is unknown but until further evidence is available, standard MRI and MRV should be carried out in any patient before the diagnosis of IIH can be given.

Prediction of intracranial hypertension may be possible by the trained neuroradiologist. Slit-like ventricles on neuroimaging are neither sensitive nor specific for IIH. Instead, other signs of elevated CSF pressure on MRI have been recognized, i.e. partially empty sella (70%), flattening of the posterior sclera (80%), dilation (45%) or tortuosity (40%) of the optic nerve sheath or gadolinium enhancement of the optic disc (50%) (154).

Cerebral angiography is not generally used for diagnosis of IIH or cerebral venous sinus thrombosis. Although superior in visualizing the rare, isolated cortical venous thrombosis, there is good correlation between MRV and angiography in sinus involvement (149).

## Cerebrospinal fluid

Cerebrospinal fluid composition is normal with no evidence of pleocytosis or abnormal glucose concentration. The protein content is either within or below the normal range (155–157).

## Differential diagnosis

IIH is still a diagnosis of exclusion. Several conditions can present with signs of raised intracranial

pressure alone (Table 4). A thorough evaluation is therefore mandatory. Atypical patients, i.e. men, children and non-obese women, are found, but secondary causes are fairly common. Even elevated CSF pressure in the young, obese woman should be considered as symptomatic until an elaborate clinical and paraclinical examination has been performed.

## Diagnosis

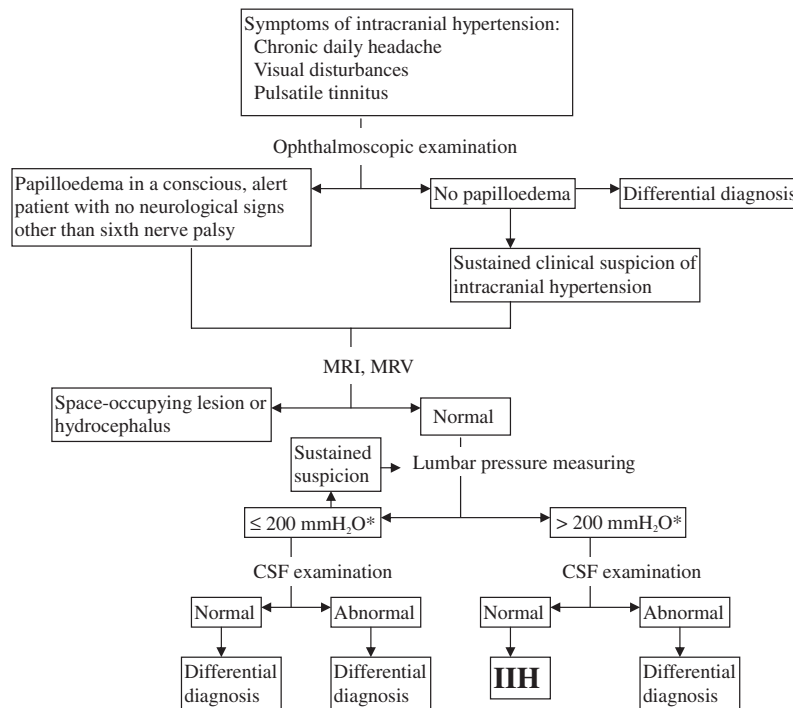
The diagnostic clues are to be found in the history. Patients, particularly obese young women, usually present with symptoms of increased ICP, i.e. a pressing headache that is unrelieved by standard therapy, pulsatile tinnitus or TVOs. It is also important to emphasize that a patient may experience more than one type of headache. The presence of pre-existing primary headache, i.e. migraine or tension-type headache, may obscure the picture. However, IIH is not always associated with either headache or visual and auditory disturbances. The risk of extended delay in diagnosis is not negligible.

Since certain medications have been associated with IIH (Table 2), any medical treatment should be reviewed and stopped if possible and the clinical effect assessed. In chronic cases the patient's current approach to headache treatment is also important since many headache sufferers overuse analgesics. Excessive use of these agents can produce withdrawal or rebound headaches and thus camouflage the effectiveness of later treatment.

An algorithm for diagnosis is suggested in Fig. 1. Clinical examination, including a general medical examination as well as a thorough neurological and

**Table 4** Differential diagnosis of idiopathic intracranial hypertension

Vascular diseases	Circulatory
Cerebral venous sinus thrombosis	Hypertension
Arteriovenous malformations	Congestive heart failure
CSF hyperviscosity	Neoplasms
Guillain-Barré	Gliomas
Spinal cord tumour	Meningeal carcinomatosis
Infection	Leukaemia
Syphilis	Others
Meningitis/encephalitis	Respiratory disease with CO <sub>2</sub> retention
Sinusitis/otitis media	Sleep apnoea syndrome
Toxicity	
See Table 2	



**Figure 1** Suggested diagnostic algorithm for idiopathic intracranial hypertension. \*200 mmHg in the non-obese, 250 mmHg in the obese.

ophthalmological examination, is mandatory and serves to exclude most other neurological disorders. Papilloedema will usually be found. All patients should be evaluated with fundus photography and perimetry in order to exclude pseudopapilloedema and determine visual status. Normal optic discs are insufficient to exclude the presence of intracranial hypertension. Whereas visual disturbances are rarely seen in IIH patients without papilloedema, significant predictors apart from headache include pulsatile tinnitus [odds ratio (OR) 13] and obesity (OR 4.4) (158). Any patients with symptoms of increased ICP or chronic daily headache that are unrelieved by standard management should be further evaluated by neuroimaging and lumbar puncture. A normal MRI is required for diagnosis and must also include MRV until further evidence is available.

Measurements of opening lumbar pressure must be prior to CSF tapping and suggestions for CSF analysis are given in Table 5. A repeat lumbar puncture is indicated if opening pressure is absolutely normal irrespective of clinical features of increased intracranial pressure. Monitoring ICP with an epidural, intraventricular or an intradural lumbar transducer for at least 6–24 h demonstrating periods of increased ICP and pathological pressure wave activity is occasionally needed in order to confirm

**Table 5** Recommended laboratory tests to exclude conditions mimicking idiopathic intracranial hypertension

Blood tests	Cerebrospinal fluid studies
Complete blood count	White blood cell and differential counts
Erythrocyte volume	Red blood cell count
Haemoglobin	Total protein
Sedimentation rate	Glucose
Full procoagulant profile	IgG index
K, Na	Quantitative protein electrophoresis
Creatinine	Borrelia, HSV, syphilis markers
ALAT	Possible tumour markers and cytology
TSH, T <sub>3</sub> , T <sub>4</sub>	

the diagnosis. Demonstrating increased CSF outflow resistance ( $>9.1 \text{ mmHg min}^{-1} \text{ ml}^{-1}$ ) at lumbar infusion test also helps to uphold the suspicion that intracranial hypertension exists despite normal CSF opening pressures, although it is not included in the present IHS criteria.

## Treatment

Too little of the pathophysiological mechanisms in IIH is known for the treatment to be causal. The treatment is symptomatic focusing on lowering the

CSF pressure, thus preventing visual defect development and disabling headaches. Both medical and surgical interventions exist but comparative randomized, prospective studies of the treatment strategies are lacking. Search for further treatment strategies is urgently needed.

Weight loss as a way of lowering ICP in the obese should be advocated (118, 121, 159, 160). In practice, weight loss can be difficult to achieve but encouragement, professional dietary counselling and even regular weight controls may be successful.

The carbon anhydrase inhibitor, acetazolamide, is usually the first-line drug in treatment and probably acts by reducing the CSF production and thus ICP. The effective dose is individual. In our experience an initial dose of 250 mg twice a day gradually increasing to a daily dose of 1000–1250 mg is recommended. Some patients require even higher doses, whereas others have no response or may be treated at lower doses because of unacceptable side-effects. Side-effects, generally acroparaesthesias, are dose-dependent. Less common are nausea, anorexia, hypokalaemia and nephrolithiasis.

When acetazolamide is insufficient or intolerable, a supplement or, if necessary, a replacement with the diuretic furosemide (40–120 mg/day) combined with potassium should be considered. Furosemide may reduce increased ICP but the mechanism is unclear (161). Although the effect of furosemide has never been evaluated in IIH patients, it seems to be much less potent than acetazolamide.

Topiramate, a relative new anticonvulsant, also inhibits carbonic anhydrase at clinically relevant doses (162). Clinical support of its effect in treatment of IIH has recently been reported in open series (69, 163) and it may now be considered as a second-line drug. However, further studies are necessary to confirm the significance of the drug in treating IIH. Although its inhibitory effect may be less potent than that of acetazolamide, another reason to consider topiramate is the weight loss, which is a frequent, and in IIH, usually a welcome side-effect.

Oral corticosteroids as a short-term treatment can be considered in acute severe cases in which up to 1 mg/kg for 2–6 weeks is reported to be effective (126, 164). However, due to the possible rebound effect and the multiple side-effects, especially unwanted weight gain, long-term treatment with corticosteroids can no longer be recommended.

Symptomatic headache treatment with analgesics is also a challenging task. Paracetamol as well as non-steroidal anti-inflammatory drugs are frequently used but should be prescribed with precaution due

to the risk of medication overuse headache (165). In such cases, medicine weaning should be considered before any optimal pain therapy or pressure reduction therapy can be expected.

Although medical therapy is generally successful, acute surgical pressure-reducing therapy is indicated when symptoms, especially vision deterioration and disabling headaches, are refractory to medical treatment. Severe unacceptable side-effects to medical treatment or a rapidly progressive vision loss also warrant surgical intervention. Any awaiting policy before recommending surgery is erroneous.

Two surgical principles are used, either CSF shunting or direct decompression of the optic nerves. The lumboperitoneal (LP) shunt has traditionally been preferred rather than ventriculoperitoneal (VP) shunt because of a claimed difficulty in cannulating the normal sized lateral ventricles and to avoid the possible risk of intracerebral haemorrhages. CSF shunting is usually an effective symptomatic therapy in IIH (166–170). Symptoms and signs of progression of visual deterioration cease. However, a significant problem is mechanical shunt dysfunctions and infections. Shunt revisions are often needed repeatedly with a revision rate per shunt-year of 0.30–1.44 (171–173). Typical complications are shunt dysfunction (55%) and overdrainage (2–25%), but infections (1%), abdominal pain and iatrogenic Chiari I malformation (0–7%) are also seen (171).

Reliable comparative data of VP and LP shunting are limited (166). VP shunts seem to be associated with a lower risk of shunt obstruction and revision than LP shunts (166, 167). VP shunting also avoids the risk of iatrogenic Chiari malformation (166), while the risk of overdrainage is similar to LP shunts (166). Placement of the VP shunt is generally easy. Lateral ventricle can usually be cannulated using standard external landmarks or simple assist devices (174). If the ventricular system is very small, stereotactic surgical navigation enables accurate targeting of the ventricle (171).

Optic nerve sheath decompression surgery for IIH has previously been advocated (175, 176). Fenestration of the optic nerve sheath creates a local reduction of the pressure around the nerve, whereas intracranial hypertension presumably persists. Thus, while visual disturbances are treated, other signs of raised CSF pressure may be unchanged unless the fistula is sufficiently large to lower the pressure of the whole cranial cavity. Up to two-thirds of successful operations are accompanied by relief of headache. Fenestration shows initial improvement or stabilization of

visual function in the majority (68–100%) (175–177). Severe vision loss and chronic papilloedema are less likely to improve and further progression of visual deterioration occurs more often in this subgroup. Postoperative complication rate is high and reported in up to 50% of the eyes (178). Even though most complications are temporary (29%) or minor [i.e. pupillary dysfunction (11%)], a poor visual outcome occurs in 1.6–2.5%, commonly due to central retinal artery occlusion (178). Up to 32% of eyes experience deterioration in visual function after an initial successful fenestration (177). Although repeated surgery can result in subsequent visual improvement, surgery is difficult and more often accompanied by complications such as scarring and fibrosis. Adjunctive mitomycin in decompression surgery for wound healing modulation has been proposed to be associated with a less frequent and less complicated repeat surgery (179), but reliable comparative data are lacking.

Repeated lumbar punctures have previously been advocated but may now be considered as obsolete and can not be recommended. The pressure-reducing effect of spinal tapping is short-term and quickly resolves when the removed CSF is replaced.

### Follow-up

During the course of the disease treatment efficiency should be evaluated with regular automated perimetry testing in order to assure stable visual function (143), preferably every second week in the beginning increasing to one per third month, when the condition stabilizes. Any progression of visual defects must be met with a more aggressive treatment policy. Clinical symptoms alone may not be sufficient for assessment of disease severity.

### Prognosis

Spontaneous recovery from IIH is common. Until recovery, the symptoms can usually be controlled by medical treatment. Sørensen et al. reported the cessation of symptoms in 70% of IIH patients within 3 months of medical treatment (142). Johnston and Paterson described a recovery from headache and TVO in 84% and 78%, respectively, after 2 months (122). Up to a quarter of IIH patients experience a more protracted course of symptoms (142).

Current knowledge of the duration of the condition is limited and seems to be highly individual. A recent retrospective study of 54 IIH patients described an average treatment duration with aceta-

zolamide of  $13.9 \pm 11.9$  months, ranging from 1 to 60 months (180). However, chronic course of IIH with chronic severe headache and visual disturbances for years is not uncommon and constitutes a major therapeutic problem, especially in specialized headache clinics. In these cases, neurosurgery intervention in spite of normal visual field examination may be the only resolution.

Even after many years without symptoms, recurrence is not unusual. Weisberg et al. reported a recurrence rate of 10% during 1 year of follow-up (126). Johnston and Paterson also reported a recurrence rate of 10% within a time span from 4 months to 14 years (122). Recently, Kesler et al. described a 40% risk of recurrences during a mean follow-up of 6.2 years, range 2–28 years (180). Twenty-one per cent of the patients had more than two episodes (180), suggesting that lifetime treatment may be necessary in a subgroup of IIH patients.

Apart from the disabling severe headache, cognitive dysfunction and visual disturbances seen in some patients on a chronic basis, permanent loss of visual function is the most serious complication in IIH. Permanent visual field defects are common. Rowe (143) has noted a normal visual field outcome in only 43% patients during the 3 years of follow-up. In 40% of the patients the defects were mild and asymptomatic, whereas 9% experienced severe visual field defects. Severe defects are often combined with a visual acuity of less than 20/40 (124). Up to 5% of patients develop blindness in one or both eyes, the risk of which is related to duration of papilloedema and rate of developing optic atrophy (124, 125).

### Conclusion

IIH is a diagnosis of exclusion that has been perplexing health professionals for decades. Complete understanding of IIH still eludes us. Advances in diagnostic neuroimaging techniques and application of manometry recordings, particularly in relation to venous sinus pathology, have succeeded in demonstrating underlying causes in some cases conventionally classified as IIH. A coexisting group of IIH patients with normal sinus pathology may also exist. Patients with venous outflow abnormalities should not be classified as IIH.

IIH usually resolves after a few months, but the risk of visual deterioration is considerable and some patients experience a chronic disabling course for years that limits their capacity to work and to participate in social life. No causal treatment is yet known for IIH and existing treatment is

symptomatic and rarely completely sufficient to render all patients asymptomatic.

It is clear that a sufficient search for secondary causes of intracranial hypertension is mandatory and, in the context of the significantly higher role of venous sinus disease in the origin of IIH than has previously been recognized, we recommend that MRV become a routine part of the work-up. The recognition of sinus thrombosis has crucial therapeutic implications as management is completely different from IIH and endovascular treatment, i.e. thrombolysis and stent placement are promising (112, 181–184), although yet experimental. Experimental pathophysiological studies as well as controlled clinical treatment studies are urgently needed in order to optimize the biological understanding and therapy.

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