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REVIEW

An update on idiopathic intracranial hypertension in adults: a look at pathophysiology, diagnostic approach and management

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Abstract

Idiopathic intracranial hypertension is a neurological syndrome determined by a rise in intracranial pressure without a detectable cause. Course and prognosis may be changeable, requiring a multidisciplinary approach for its diagnosis and management. Although its precise pathogenesis is still unknown, many studies have been carried out to define the possible causal and associated factors, such as retinoids, steroid hormones, body mass index and recent weight gains, cytokines and adipokines levels. The clinical presentation can be variable including chronic headache, disturbance of vision, diplopia and tinnitus. Even if papilloedema is considered the most specific sign, it could not be observed in more than 5% of patients during the evaluation of the fundus oculi. Neuroradiological signs acquire greater importance in patients who do not present papilloedema and may suggest the diagnosis of idiopathic intracranial hypertension. Other assessments can be useful in the diagnostic process, such as optical coherence tomography, visual evoked potentials, ocular ultrasonography and fundus fluorescein angiography and autofluorescence. Nonetheless, cerebrospinal fluid pressure measurement is required to establish a definite diagnosis. Management may be different, since surgical procedures or lumbar punctures are often required when symptoms develop rapidly leading to a loss of visual function. Apart from these cases, patients can be treated with a pharmacological approach and low-calorie diet, but they also need to be monitored over time since relapses years later are not uncommon.

Keywords Idiopathic intracranial hypertension · Pseudotumor cerebri · Papilloedema · Transverse sinus stenosis · Acetazolamide

Introduction and epidemiology

Idiopathic intracranial hypertension (IIH) is a clinical condition characterized by an increase of intracranial pressure (ICP) in absence of any identifiable causal factor. This implies that any medical condition, venous abnormalities and drug intake or exposure which could cause a secondary development of intracranial hypertension must be excluded to define the diagnosis (Table 1). Incidence in general population is about 0.9/100.000/year in West countries, but it grows up to 3.5/100.000/year considering a female population ranging from 15 to 44 years. It is even greater if just those women aged 20–44 years exceeding ideal weight over 20% are considered, amounting to 19/100.000/year [1]. Interestingly, despite previous studies stated that no ethnical background exists, a lower incidence has been noted in Asian countries (0.03/100.000/year), interpreted as the result of the different worldwide prevalence of obesity, ten times greater in the USA in comparison to Asian states [2, 3]. It is quite clear from these data that female sex and obesity seem to be strongly associated with IIH. Prevalence in men has been estimated approximately at 9% of definite cases of IIH: such a gender difference does not exist in pre-pubertal timing, suggesting a possible role of sexual hormones in the determinism of the condition in women of child-bearing age. Like women, men suffering from IIH are mostly obese, but older at diagnosis with an average age of 37 years vs 28 years in women [4]. Furthermore, it is a rare disease in the elderly and in children under the age of 3 years, with an age-specific incidence which goes from 0.17/100.000 in patients aged 1–6 years to 0.75/100.000 in 7–11 years to 1.32/100.000 in 12–16 years [5].

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Table 1 Causes of secondary intracranial hypertension

Secondary intracranial hypertension
Endocrine diseases (Addison, hypoparathyroidism)
Sleep apnea
Drugs (tetracycline, doxycicline, sulfa drugs; lithium; chlordecone)
Retinoids exposure and hypervitaminosis A
Hormones exposure (hGH, thyroxine, levonorgestrel, anabolic steroids)
Withdrawal from chronic corticosteroids
Renal failure
Turner syndrome
Down syndrome
Dural venous sinus thrombosis
Bilateral jugular vein thrombosis or surgical ligation
Central venous hypertension due to heart failure
Arteriovenous malformations or dural fistulae with high flow
Superior vena cava syndrome
Middle ear or mastoid infection
Previous meningitis or subarachnoid hemorrhage
Guillain–Barre syndrome or intraspinal tumors
Large and slow-growing CNS mass

hGH human growth hormone, *CNS* central nervous system

Pathophysiology and associated factors

A dysregulation of cerebrospinal fluid (CSF) dynamics is supposed to be involved in the pathophysiology of this condition, but the precise mechanism is still not known: it may involve hypersecretion of CSF at the choroid plexus, reduced reabsorption at the arachnoid granulations and abnormal venous pressure gradients. A lot of hypotheses have been formulated and lots of factors investigated as possibly associated.

As concerns obesity, increasing levels of body mass index (BMI) correlate with a major risk for this condition and with a more severe visual outcome. Even a mild weight gain between 5% and 15% in both obese and non-obese patients, especially if occurred within the 12 months prior to symptom onset, is associated with a greater risk of disease [6, 7]. Moreover, increases in BMI after IIH resolution are probably a risk factor for recurrence [8].

It has been supposed that a central body fat distribution may determine an increase in central venous pressure and consequently a raised venous ICP obstructing CSF reabsorption [9]. However, some studies have found a more prevalent lower body distribution of fat than abdominal one in obese women with IIH compared with same-aged obese women not suffering from the disease [10]. Another theory supports occult venous micro-thrombosis in obese patients as a causative factor for interruption in distal venous circulation, impeding CSF drainage with a similar mechanism. Moreover, elevated levels of fibrinogen, D-Dimer, factor VIII, factor IX and factor XI have been found in IIH obese patients compared with non-obese ones [11]. Finally, a neuroendocrine pathway could be considered, involving different cytokine and adipokine profiles in obese patients which may modulate CSF secretion. Some clinical studies have detected elevated levels of leptin in obese IIH patients, read as a sign of central leptin resistance. It has been supposed, thus, that chronic elevated levels of leptin can increase CSF secretion throughout an increased activity of NA^+/K^+ ATPase in the epithelium of choroid plexus [12].

The role of incretins in the homeostasis of CSF dynamics has been proved in rats [13] and has led to the formulation of the glucagon-like peptide-1 (GLP-1) receptor agonist exenatide, whose effects and safety are under investigation in the IIH Pressure Trial (ISRCTN12678718) [14]. Indeed, along with stimulating glucose-dependent insulin secretion and favoring weight loss, GLP-1 has proved to be involved in both renal and CSF homeostasis through the modulation of Na^+ reabsorption, being, respectively, expressed in both renal proximal tubule and in human choroid plexus [15].

Since IIH is predominantly diagnosed in obese females of child-bearing age, the female gender seems to be a definite associated factor for IIH, suggesting an involvement of steroid hormones. Hormonal levels in serum and CSF of patients with IIH have been evaluated in several studies, but results have not been consistent [16, 17]. Currently, the role of 11β-hydroxysteroid dehydrogenase (11β-HSD) type 1, which converts inactive cortisone to cortisol, is under investigation. Being expressed in choroid plexus epithelium, it could increase the availability of CSF cortisol and enhance the stimulation of mineralocorticoid receptors, leading to a major activity of NA^+/K^+ ATPase and CSF secretion [12]. Interestingly, its activity increases in subcutaneous fat in obese people and decreases in parallel to the reduction of ICP after substantial weight loss in obese IIH patients [18]. The efficacy and safety of the 11β-HSD inhibitor AZD4017 is currently under investigation in IIH Drug Trial (NCT02017444), the first phase 2 placebo-controlled trial in IIH [15, 19].

The association between Obstructive Sleep Apnea (OSA) and IIH has been proved, but explained with a high prevalence of obesity in both populations, especially in men [4]. Indeed, both the severity and prevalence of OSA in IIH patients do not seem to be greater than expected considering age, sex, race, BMI and menopausal status [20]. It has been supposed that transient increases of ICP during apneic episodes, due to hypercapnia and vasodilation response, may become sustained because of the compression of cerebral venous sinuses [21]. Even though most of findings do not suggest that OSA has a causative role for IIH, it would be

useful to understand if treatment with CPAP can reduce IIH in these patients, since results obtained from clinical studies have not been consistent yet. However, an improvement of OCT measurements and the normalization of CSF opening pressure (CSF_{op}) were reported in a 10-year-old boy with IIH and pre-existing OSA, treated with septoplasty surgery with resolution of sleep apnea episodes and daytime somnolence [22].

Vitamin A and retinoids have also been under evaluation as possible associated factors, since it is known that an excessive intake or chronic lower doses of vitamin A can induce a secondary intracranial hypertension. Retinol, bound in the circulation in a complex with retinol-binding protein and transthyretin, is produced in high levels in the choroid plexus. Uptaken into the cells and converted to all-trans-retinoic-acid, it could modulate gene expression in the arachnoid granulation cells, in ependymal or glial cells, reducing CSF reabsorption. It has been suggested that such a mechanism involves molecules as Aquaporin-1, expressed in choroid plexus epithelium and involved in CSF production, and Aquaporin-4 (AQP-4), expressed in ependyma and astrocytes and maybe cooperating in CSF reabsorption [23]. Although some previous studies disagree in highlighting differences in serum and CSF vitamin A profile between IIH patients and controls [24–26], a more recent investigation has highlighted unexpected lower levels of serum all-trans-retinoic-acid in untreated IIH patients compared with controls of similar age, gender and BMI at baseline. Interestingly, treatment with Acetazolamide (ACZ) can cause in itself an increase in CSF all-trans-retinoic-acid in IIH patients compared with placebo [27].

No association has been confirmed between IIH and pregnancy, thyroid diseases, iron deficiency anemia and antibiotic intake [28]. As for hormonal contraceptives, the hypothesis of an association with IIH has long been a matter of debate [29–32]. Currently, there is not a contraindication for the use of such medications, as reported in the latest guidelines on management [33].

Finally, CSF reabsorption has been hypothesized to be impeded by an altered venous outflow due to venous sinus obstruction [34]. Arachnoid granulations, protruding into cerebral venous sinus, allow CSF resorption, which is more significant into the superior sagittal sinus and hampered in case of increased venous sinus pressure [35]. Such a condition may occur when bilateral transverse sinus stenosis (BTSS) exists, as reported with a prevalence of 65–100% in patients with IIH [36–38]. The narrowing is usually located in the mid-lateral part of the transverse sinus, determining a pressure gradient between the proximal and the distal section of the stenosis and higher pressure values in the sagittal sinus, correlated with an increase of ICP [39]. Despite the treatment of the stenosis through a stent placement has proved to be effective in reducing ICP [40, 41], the genesis of BTSS is not equally clear. Venous internal large trabeculae or other filling defects as giant arachnoid granulations could determine a narrowing from inside, while the increased ICP could press on venous walls from outside [42].

A physiopathological model has been proposed by De Simone and coworkers [43], considering the increase of ICP as a result of an excessive collapsibility of dural sinuses. Indeed, such a condition leads to an increase of sinus pressure along with the external physiological ICP fluctuations, impeding CSF outflow with consequent further increase of ICP. In this perspective, the overmentioned factors (trabeculae, giant granulations) and conditions that increase central venous pressure (OSAS, rapid gain of weight) may trigger the loop. This could explain the efficacy of therapeutic strategies which directly expand the sinus, such as stenting [44], or which promptly reduce CSF pressure (pCSF) pushing on sinus wall, such as lumbar punctures (LP) [45] or CSF shunting [46]. Such an intervention allows the reduction of dural sinus pressure and reestablishes a favorable gradient to CSF outflow. Therefore, BTSS would not be simply a consequence of an increased ICP but also a causative factor, and transverse sinus stenting would represent an etiological therapy.

Last but not least, the involvement of BTSS in determining IIH is debated, since it is considered by some authors as a cause of "vascular" intracranial hypertension, a secondary condition that cannot be denominated as "idiopathic" [47]. For the same reason, intracranial hypertension due to cerebral venous thrombosis should be ruled out before taking into consideration IIH, despite clinical findings, CSF_{op} values and comorbidities do not seem to be substantially different [48].

Still little explored is the role of the "glymphatic system", which seems to be responsible for the removal of metabolites from the brain parenchyma. It seems to operate allowing both CSF recirculation along paravascular spaces, communicating with the interstitial fluid, and CSF drainage into lymphatics across the meningeal sheets of spinal and cranial nerves [49]. According to Lenck et al., this may be the main mechanism determining CSF outflow in normal conditions, resizing the contribution of arachnoid granulations [50]. A glial barrier, consisting of contiguous astrocytic end-feet, separates the interstitial compartment from paravascular spaces, allowing fluid exchanges through the high-density expression of AQP-4 water channel proteins [51]. According to this model, IIH could be explained by a glymphatic dysfunction due to an overload of interstitial fluid, which fails to move forward into the paravenous spaces. This may be the result either of a loss of AQP-4 or of the increased permeability of the blood–brain barrier during perivascular inflammation, which is chronic in obese patients, leading to an expansion of interstitial compartment [49].

Considering common physiopathological mechanisms, several studies have been carried out to explore potential comorbidities. Based on the hypothesis of an androgen excess in the pathogenesis of IIH [52], a recent study has been recently carried out in the United Kingdom to explore the risk of cardiovascular diseases among IIH patients. Compared with healthy controls of similar BMI, age and sex, IIH patients showed twice the risk of cardiovascular disease [53]. Speculating a shared neuroendocrinological genesis, a recent study investigated the prevalence of psychiatric comorbidities among a cohort of IIH patients, which were pre-existing in 45% of them and mainly represented by major depressive disorder. Results of this study also detected worse treatment outcomes among IIH patients with psychiatric disorders and a greater prevalence of empty sella among them than in the other group of IIH patients [54].

The association between IIH and primary headaches, especially migraine, is still debated. Whether migraine is a comorbidity, an independent risk factor for the developing of IIH, or a secondary headache due to IIH in patients who are not otherwise predisposed to migraine itself is not entirely clear. It is known that up to 70% of patients with IIH and headache as presenting symptom exhibit migraine features and up to 45% have a personal history of migraine [55]. Furthermore, a prevalence of IIH without papilloedema (IIHWOP) by 10–14% was found among chronic migraine sufferers [56] and it is well known that migraine and IIH share common risk factors, as obesity, female gender and sleep disorders [57, 58]. IIH is thought to be able to reduce the migraine threshold in both patients with pre-existing and new-onset migraine [59]. Moreover, it has been speculated that IIH can promote pain chronicization in patients suffering from pre-existing episodic migraine. Through a continuous stimulation of afferent nociceptors to the congested and distended venous sinuses, a central sensitization may occur resulting in increased frequency and duration of migraine episodes [56]. This could lead to consider IIH as the cause of the high frequency and poor treatment responsiveness of migraine rather than of migraine in itself [60] and to explain why headache can persist even after the reduction of CSF_{op} [59]. Subsequently, it can be particularly challenging to make a diagnosis of primary headache or secondary one in patients with IIH who exhibit such a symptom. According to the latest version of the International Classification of Headache Disorders (ICHD) [61], a headache resembling a primary one should be considered as secondary to IIH whether it is new onset and a close temporal relationship with the intracranial disorder exists. If instead the headache was pre-existing to IIH but worsened under the increase of CSF_{op}, both a diagnosis of primary headache and of headache attributed to IIH should be made [62].

Clinical features

People affected by IIH are usually referred to the neurologist, because they complain of headache, the most common presenting symptom in up to 84% of patients [63]. According to the ICHD-2 criteria of the International Headache Society (IHS), headache attributed to IIH should be characterized by a progressive course and either daily occurrence, constant non-pulsating pain or exacerbation by coughing or with the Valsalva manoeuvre [64]. It is also often referred to as commonly bilateral, frontal or retroocular, showing similarities with tension-type headaches [65], but up to 70% of headache sufferers exhibit migraine features, including unilateral throbbing pain with nausea and photophobia [66]. Patients with pre-existing migraine may exhibit different headache features when developing symptoms due to IIH [59, 62]. Moreover, according to ICHD-3 criteria, not only a new-onset headache, but also a significant worsening of a pre-existing one can be attributed to IIH, whether developing along with the increase of CSF_{op} values [61]. Despite the improvement and even the complete resolution of the symptom would be expected after the normalization of CSF_{op} values [64], the persistence of headache has been reported, sometimes showing little correlation between its severity and frequency and CSF_{op} values [59]. Results from the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT) pointed out that headache, particularly with photophobia, was the main factor having a negative impact on general and visual quality of life [55]. Several questionnaires have been used to assess patient reported outcomes in patients with headache disorders. Among them, Migraine-Specific Quality of Life Questionnaire, Patient Perception of Migraine Questionnaire and the Headache Impact Test 6-item have been indicated as reliable tools to assess the frequency and severity of headache and its impact on quality of life [67].

Disturbance of vision is the second most frequent symptom. Visual loss is reported by 32% of patients, occurring with variable visual field defects, mainly an enlargement of the blind spot with a partial inferior arcuate defect [63]. In a recent study, assessing visual field defects in a cohort of 39 patients with IIH and just mild central visual loss, 18% of patients had peripheral visual field defects alone, with normal findings in central visual field. Peripheral temporal defects were the most frequent ones, globally detected in 46% of patients, half of which with inferior temporal deficits, followed by infero-nasal, supero-nasal and arcuate defects [68].

Visual acuity is assumed to be normal in up to 2/3 of cases, except in patients with severe visual loss or damage in the papillomacular region [63]. Men are more likely to report visual disturbances at onset of symptoms than

headache, unlike women [4]. Up to 68% of patients complain about transient visual obscurations, non-specific transient episodes of unilateral or bilateral visual loss, due to a transient ischaemia of the optic nerve head (ONH) caused by an increased tissue pressure. They usually last less than a minute and are often precipitated by postural changes, with full visual recovery [69]. Less than 20% of patients refer diplopia as presenting symptom and usually in horizontal plane, since generally due to a 6th cranial nerve (c.n.) palsy [63]. Tinnitus, which is more often bilateral, pulsatile and synchronous with heart rate, can be variable in frequency, from daily to monthly. Several patients refer pain with radicular pattern, dizziness and affective or cognitive alterations [63] (Table 2).

According to Friedman revised diagnostic criteria [70], a normal neurologic examination is required for diagnosis, except for c.n. dysfunctions. These ones more often involve the 6th c.n., with esotropia in 3% of cases, and less frequently the 3rd, 4th or 7th c.n. Olfactory impairment has also been described in a cohort of patients with IIH compared to healthy controls [71]. It is important to underline that the patient's mental status must be normal. IIH may also have an impact on neuropsychological functions, as explored by Zud and coworkers [72]. Taking account of age and education, patients with IIH had global sub-standard scores, with the lowest scores in tests examining attention and visual spatial processing.

Papilloedema is the most specific sign of intracranial hypertension and it can be observed during the evaluation of the fundus oculi. It is an optic disc swollen due to the raised pressure exerted on the optic nerves, causing an impaired axoplasmic flow. The altered venous outflow from the retina determines at first the loss of previously observed venous pulsations, the engorgement of capillaries and veins on the disc surface with color change from yellowish-pink to red, until the elevation of the optic disc, splinter and flame hemorrhages and cotton-wool exudates in the retinal nerve fiber layer (RNFL). Four stages can be recognized: early, fully developed, chronic and atrophic papilloedema [73]. In clinical practice, the Frisén scale has been used to get a formal grading of papilloedema, even if it requires a certain expertise and is burdened by a limited reproducibility. Papilloedema is usually bilateral, despite up to 7% of patients show an asymmetric condition defined as a 2-grade difference at the Frisén scale [63]. A few cases of pseudo-Foster Kennedy with one-sided optic atrophy and papilloedema in the contralateral eye have been described, thought to be asymptomatic up to 25% [74]. Papilloedema can develop rapidly with permanent visual loss in up to 10% of cases [65] and it is often difficult to distinguish from pseudopapilloedema. The latter is not due to an increase in ICP, but to several potential conditions, such as the presence of ONH drusen, hypermetropia, tilted disk, congenital abnormalities, oblique insertions of optic nerves [75].

The condition of IIHWOP is characterized by a 0-grade at the Frisén scale. In a cross-sectional analysis by Digre et al. [76], the prevalence of IIHWOP in a sample of 353 patients was 5.7%. Significant differences in age at onset, BMI, history of migraine and prevalent symptoms between the two groups have not been detected. Patients with IIHWOP, though, exhibit a major prevalence of photopsia and anomalous venous pulses, a minor prevalence of diplopia and enlargement of the blind spot and minor values of ICP despite pathological pCSF patterns, compared with IIH with papilloedema (IIHWP).

Finally, some patients with IIH can be asymptomatic, or even have symptoms of intracranial hypotension, oto- or rhino-liquorrhea, which are rare, but suggestive signs of IIH. Such a clinical condition may occur when chronically raised ICP leads to CSF leaks through remodeling of the skull base, mainly involving ethmoid and sphenoid lateral recess, with subsequent meningo-encephaloceles [77, 78]. Such cases are mostly diagnosed when symptoms of IIH occur after surgical repair of the leak, leading to a new increase of ICP, or when CSF leaks itself recurs after surgery [78, 79].

Table 2 Usual clinical symptoms and signs in patients with IIH

When should we suspect IIH?
Chronic daily headache, often with migraine features (unilateral throbbing pain with nausea and photophobia) or bilateral and exacerbated by coughing or with the Valsalva manoeuvre, especially in women
Transient episodes of unilateral or bilateral visual loss, lasting less than a minute, often precipitated by postural changes, followed by full visual recovery, especially in men
Visual loss with variable visual field defects
Diplopia in horizontal plane
Bilateral pulsatile tinnitus, variable in frequency
CSF rhinorrhea or otorrhea
Bilateral or rarely unilateral papilloedema even in asymptomatic patients in patients with normal mental status

IIH idiopathic intracranial hypertension, *CSF* cerebrospinal fluid

Neuroradiology

Patients suffering from chronic headache and not presenting papilloedema at the evaluation of the fundus oculi are more likely to be misdiagnosed, since the absence of the typical sign could lead not to consider the possibility of IIH. Neuroradiological signs assume a major significance in these cases, since they may suggest, but not define, the diagnosis of IIH if papilloedema or the 6th nerve palsy are absent, according to Friedman criteria [70].

An empty sella, best observed in T1 sagittal magnetic resonance (MR) sequences, can be a suggestive sign of IIH, with a sensitivity of 65% and a specificity of 95.3% according to Maralani and coworkers [80], while values of 80% sensitivity and 64% specificity have been reported in a recent study by Mallery et al. [81]. This finding, though, has also been reported in a recent study in patients with pulsatile tinnitus and lateral sinus stenosis without signs of increased ICP [82]. Due to the herniation of the subarachnoid space into the sella turcica, with the consequent flattening of the hypophyseal tissue, empty sella can be partial or total when the pituitary fossa is, respectively, filled with CSF less or more than 50% [83] (Fig. 1). A posterior displacement of pituitary stalk has also been observed in some studies [84].

Another neuroradiological sign is the posterior flattening of the eyeball with the eventual protrusion of the ONH into the vitreous humor (Fig. 2), which has 54–57% sensitivity and 97–100% specificity [80, 81]. According to Agid et al., this finding alone is able to increase 50-fold the probability of having IIH [85] and, if combined with "empty sella", levels of 75% sensitivity and 100% specificity are reached for patients who show any of the two signs [86]. Moreover, it seems that pituitary height and globe conformation may persist after ICP normalization and papilloedema resolution [84].

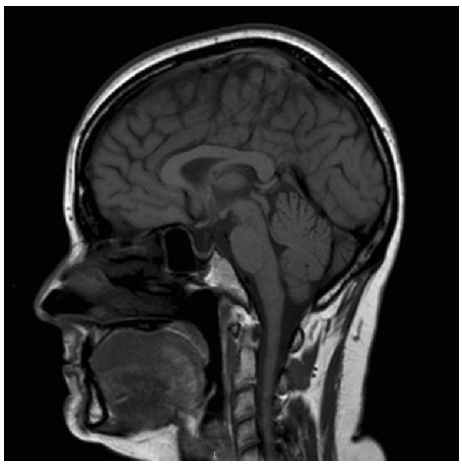


Fig. 1 MR T1-weighted sagittal image showing total empty sella, with the flattening of the hypophyseal tissue at the bottom of the sella turcica

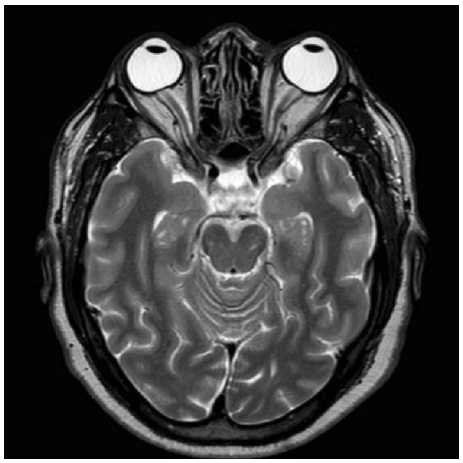


Fig. 2 MR T2-weighted axial image showing posterior flattening of the eyeballs and enlargement of the perioptic subarachnoid spaces

The posterior flattening of the eyeball can be best noted employing MR with orbits scan, just like the enlargement of the perioptic subarachnoid spaces, which shows a 51% sensitivity and 83% specificity [81]. Preliminary results showed that this last neuroradiologic sign best correlates with the impairment of colour vision and, together with intraocular optic nerve protrusion, with optic disc assessment [87].

Despite not being part of the current diagnostic criteria, the tortuosity of the midportion of the optic nerve, especially kinking in vertical plane, is a specific sign of increased ICP, increasing the odds of having IIH fivefold [85, 88]. Recently, optic nerve angle measured on both sagittal and axial planes has been proposed as a quantitative measure of tortuosity. Particularly, sagittal optic nerve angle proved to increase after ICP lowering obtained with therapeutic LP [89].

The enhancement of the optic nerve shows low levels of sensitivity, but a nearly 96% specificity [84].

Post-contrast FLAIR hyperintensity of the optic nerve and optic disc has been recently investigated, proving to predict the presence of papilloedema in patients with IIH, with a moderate correlation between the intensity of the enhancement and the severity of papilloedema [90].

Moreover, a recent study investigated the presence of potential differences in osseous optic canal size between eyes in patients with IIH and asymmetric papilloedema, but without substantial results [91].

Finally, the evidence of BTSS has gained importance since it has been identified in a relevant percentage of patients suffering from chronic headache [92, 93] (Fig. 3). In two different studies by Bono and colleagues, BTSS was identified in 9% of patients suffering from chronic tension-type headache and in 6.7% of patients suffering from chronic migraine. In both groups, the two-thirds of patients with

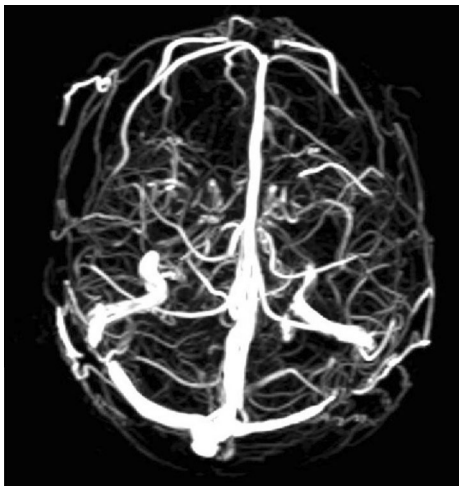


Fig. 3 MR-venography with 3DPC images showing bilateral transverse sinus stenosis

BTSS showed increased values of CSF_{op}, being diagnosed with IIH. In another study conducted among 217 patients with chronic headache, all patients with $CSF_{op} > 200$ mmH_2O displayed BTSS, which was present also in 13% of those who had values < 200 mmH_2O [94].

Maybe such results should induce to reconsider the diagnosis of a primary headache in similar cases, in favor of a diagnosis of "headache attributed to IIH" according to the latest criteria of the IHS [95]. To best detect BTSS, a MR-venography with three-dimensional phase contrast (3DPC) images setting velocity encoding (VENC) at 15 cm/s should be performed, since it has been proved to be more accurate than both 3DPC with VENC at 40 cm/s and two-dimensional time-of-flight technique [38]. In studies employing 3DPC images setting VENC at 15 cm/s, a prevalence of BTSS amounting to 65–100% has been detected among patients with IIH [36, 38, 81]. Several studies reported values of sensitivity and specificity greater than 90% each for BTSS [36, 37, 88]. According to a recent systematic review and metanalysis on MR signs in IIH, BTSS is the only MR signs among all showing not only high specificity, but also high sensitivity [84].

Infrequently, multiple sinus stenosis have been reported in patients with IIH, involving both transverse sinus and superior sagittal sinus [96]. Moreover, the presence and increased size of an occipital emissary vein, connecting the suboccipital veins with the confluence of sinuses, has been pointed out as a possible sign suggestive of IIH [97]. A combination of at least three of the aforementioned four MR features has proved to be nearly 100% specific and 64% sensitive in detecting IIH, also in patients with chronic headache but without papilloedema [81].

In addition to the overmentioned widely accepted signs, the widening of the foramen ovale has been proposed in a case–control study by Butros and colleagues, able to detect IIH with 81% specificity and 50% sensitivity setting a cut-off value of 30 mm [98]. Indeed, remodeling of the skull base may occur, due to chronically high ICP and potential cause of meningo-encephaloceles and CSF leaks as previously mentioned, mainly involving sphenoid and ethmoid bones [78], with enlargement of Meckel's cave reported in about 9% of patients [88]. Widening of jugular foramen and hypoglossal canal have also been observed among patients with IIH [99].

Finally, alterations in periventricular white matter have been detected with diffuse tensor MR imaging scans in patients with IIH. The hypothesis of a tissue compression determined by high ICP, with consequent microstructure reorganization, has been speculated and requires further investigations [100].

The presence of slit-like ventricles, tight subarachnoid space and the inferior position of cerebellar tonsils in patients with IIH has been investigated in a recent meta-analysis, showing low levels of sensitivity (6–19%) and good specificity (90–97%) [84].

It is important to recall that the presence of one or more signs significantly increases the odds of a diagnosis of IIH, even though their absence does not rule it out. Finally, MR can also be a useful monitoring for patients with IIH after treatment, particularly as the height of pituitary gland in midsagittal image and the optic nerve sheath thickness seem to be reversible morphometric MR characteristics [101].

CSF pressure monitoring

The pCSF measurement and monitoring remains one of the most important findings to establish a diagnosis of IIH. According to Friedman's revised diagnostic criteria, a $CSF_{op} > 250$ mmH_2O for adults, and > 280 mmH_2O in children, is required. Indeed, if this criterium is not respected when all others are, the diagnosis of IIH can be "probable" but not "definite" [70]. However, the detection of values ranging between 250 and 300 mmH_2O is considered as a "grey area", which has to be carefully interpreted and contextualized, since CSF_{op} values greater than 250 mmH_2O have been found in healthy people [102]. LP with CSF analysis and measurement of opening pressure should be performed in all patients with papilloedema after brain imaging and perhaps more extensively in patients with chronic headache suspected to be affected by IIH [33], despite this last indication is still debated [103].

However, the simple measurement of the height of the CSF column may be misleading, as pCSF may vary considerably with time, so the possibility to repeat LP or to perform a more invasive ICP monitoring should be taken into account if a high clinical suspicion persists [33]. Moreover,

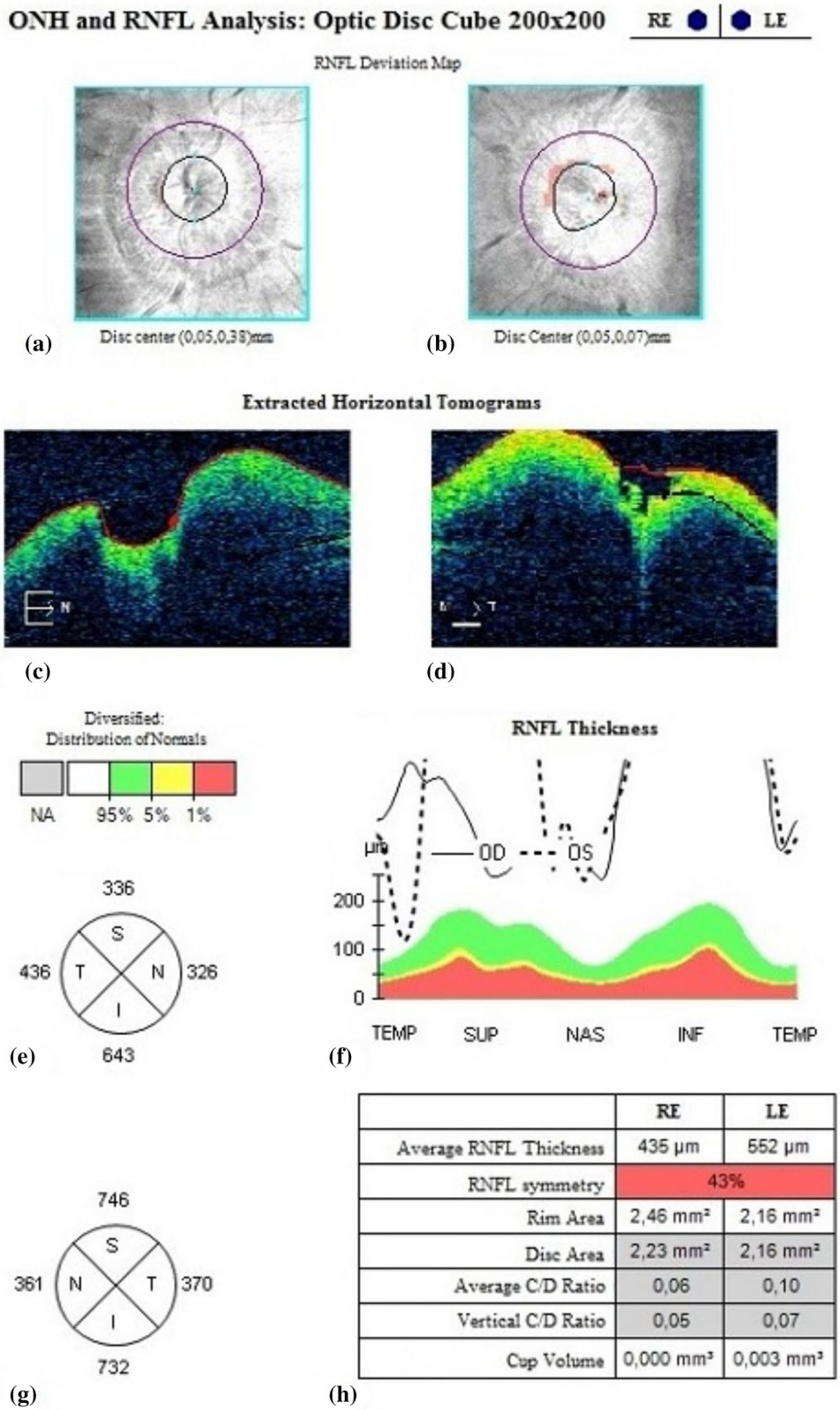
much more information than the opening pressure value can be inferred from a more prolonged pCSF monitoring, such as peak ICP, mean ICP and ICP amplitude or pulse wave amplitude (PWA), measured as the difference between the maximal and the minimal values of the pCSF during the systolic and the diastolic phase of the arterial pressure at each interval of time. Increased mean values of PWA ($\geq$54.8 mmH_2O) have been reported in patients with IIH, even in those who showed normal mean ICP values [104]. Similarly, elevated PWA values have also been observed in idiopathic normal pressure hydrocephalus responsive to shunt implantation [105], in some cases of vascular parkinsonism associated to radiological evidence of ventricular enlargement [106], in subarachnoid haemorrhage [107]. In addition, the way PWA varies along with ICP provides indirect information about the compensatory CSF regulatory reserve. On a "pressure–volume curve'', when PWA varies directly with ICP, little changes in volume produce great changes in ICP denoting a poor compensatory reserve, as observed in IIH [108]. Actually, ICP is not only influenced by the CSF component, but also by volumetric brain tissue variations and by a vasogenic constituent, both arterious and venous [109]. This last one is thought to be the most substantial in triggering an elevation in ICP in patients with IIH. All of these components contribute in determining ICP waveform, which is normally characterized by rapid and regular fluctuations, synchronous with heart and respiratory rate. However, when a depletion of the compensatory reserve occurs, abnormal pulsations can be identified, according to criteria adapted from Lundberg's original description [110]. Slow rhythmic waves characterized by an increase of ICP from 68.5 to 680 mmH_2O and a frequency of 0.5–2 cycles per minute are called B waves, reported in IIH and secondary intracranial hypertension. Differently, A or plateau waves are transitory but sustained increases of ICP lasting for 5–20 min and higher than 680 mmH_2O (or less, in case of near-plateau waves) [111]. Interestingly, abnormal pressure pulsations have been recorded during 1-h pCSF monitoring in chronic headache sufferers suspected to have IIHWOP: only those patients who effectively showed increased pCSF values reported abnormal pressure pulsations, while controls and headache sufferers with normal ICP values did not. Moreover, the entity of altered pressure parameters correlated with the likelihood of suffering from associated symptoms, as postural/nocturnal/cough-exacerbated headache, transient visual obscurations, pulsatile tinnitus, vertigo, pulsating pain [112]. In another study, continuous pCSF monitoring allowed to detect IIHWOP in patients with chronic headache, who showed normal resting pCSF values, but wide fluctuations of ICP with increased values during sleep, pathological patterns as B waves and plateau waves and a good clinical response after CSF drainage [111]. Recently, Funnell and coworkers tried to set a cut-off value able to distinguish between IIHWP and IIHWOP through a 24-h ICP monitoring, finding 10 mmHg as the minimum threshold value recorded for at least 30 min in patients with IIHWP, with 91% specificity and 48% sensitivity [113].

It would, therefore, be worthy to perform a pCSF monitoring over a period of at least an hour, to orient in case of doubts or borderline CSF_{op} values. Moreover, overnight pCSF monitoring has been proved to be useful to define patients who can be eligible for surgical CSF diversion and to assess if an implanted CSF diversion is optimally working [109].

Pioneering tools have been recently launched on the market, consisting in microsensors which can be either placed in the brain parenchyma or connected with a ventricular drain through a reservoir, allowing a continuous long-term telemetric ICP monitoring. This could allow to evaluate the advisability of a shunt placement in rapidly worsening patients with IIH or to assess ICP values and the setting of shunt valves in patients who underwent neurosurgical shunt placement [15]. Recently, a porcine model has been developed to investigate orbital CSF flow and pressure and preliminary results reported a more pronounced CSF deceleration in perioptic subarachnoid space than in other sites, especially when eye movements are absent [114].

Other assessments

Optical coherence tomography (OCT), providing cross-sectional images of the retina and allowing measurements of RNFL thickness and total retinal thickness, can be useful in patients with IIH (Figs. 4, 5) for both detecting papilloedema and its eventual reduction after treatment and monitoring chronic axonal damage. An increased peripapillary total retinal thickness is associated with increased ICP [115] and has proved to be more accurate than RNFL thickness especially in higher grades papilloedema, with a good correlation with clinical staging [116]. In such cases, oedema may impede to clearly define macular RNFL by thickening peripapillary retinal layers and to detect the structural damage to the macula [117]. In a recent study, the reduced thickness of ganglion cell complex layer has been proposed as an earlier measure of optic nerve injury [118]. Conversely, the deformation in peripapillary retinal pigment epithelium and Bruch's membrane as well seems to be useful as marker of disease activity in patients with atrophic papilloedema with scarce RNFL swelling [15]. OCT can also quantify ONH volume, increased in patients with IIH and decreased after treatment with ACZ, together with total retinal thickness and RNFL thickness [119]. With the advent of OCT angiography, ONH vascularization can also be investigated, revealing early findings of papilloedema in IIH as the presence of dilated and tortuous capillaries similar to "a tangled ball of vessels"



	RE	LE
Average RNFL Thickness	435 µm	552 µm
RNFL symmetry	43%	
Rim Area	2,46 mm²	2,16 mm²
Disc Area	2,23 mm²	2,16 mm²
Average C/D Ratio	0,06	0,10
Vertical C/D Ratio	0,05	0,07
Cup Volume	0,000 mm³	0,003 mm³

Fig. 4 OCT showing the presence of bilateral papilloedema, more prominent in the left eye, with associated retinal impairment. Images of ONH (bordered by a black line) are represented in (**a**) and (**b**), together with the area used for the measurement of RNFL thickness (bordered by a purple line). ONH swelling and consequent thickness in the right eye (**c**) and in the left eye (**d**) are better discernible looking at horizontal scans. Thickening of RNFL was seen in all quadrants (**e**–**g**). In the right eye, a mean RNFL thickness of 435 µm has been detected (**h**), particularly in the inferior quadrant (643 µm) and in the temporal one (436 µm) (**e**, **f**). In the left eye, a mean RNFL thickness of 552 µm has been detected (**h**), particularly in the superior quadrant (746 µm) and in the inferior one (732 µm) (**f**, **g**). An overview of OCT measurements is represented in (**h**). *OCT* optical coherence tomography, *ONH* optic nerve head, *RNFL* retinal nerve fibers layer

without vascular dropout [120]. A decrease in peripapillary vessel density has also been detected in patients with IIH compared to healthy controls [121]. Finally, OCT allows to monitor the chronic structural damage of the macular RNFL that occurs over time, resulting from the disc edema [117].

Since *visual evoked potentials* (VEPs) are used as indicators of the functional integrity of the visual pathway, they

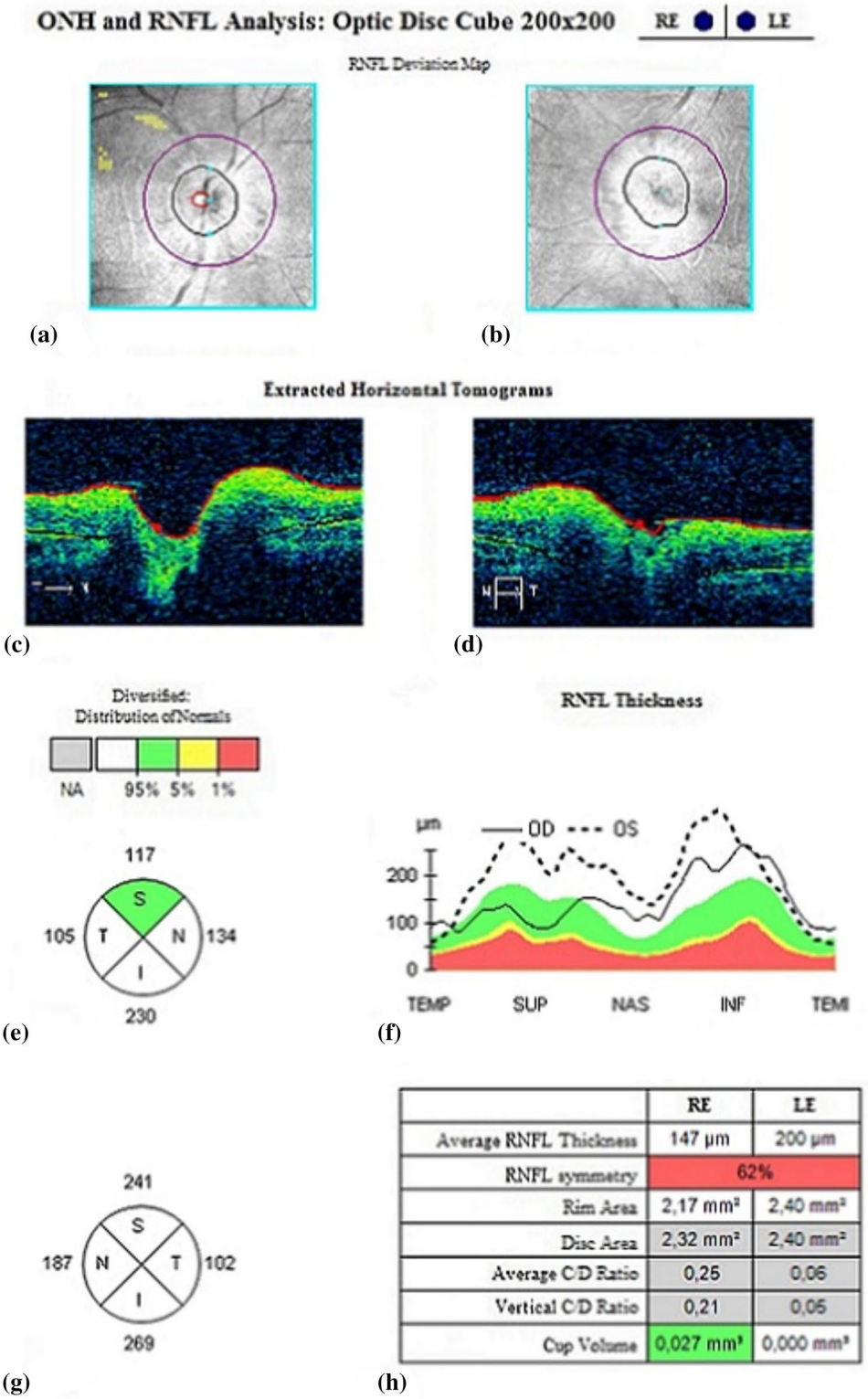


Fig. 5 OCT performed on the same patient after LP, showing the prompt effect of subtracting CSF on the reduction of papilloedema. For the description of singular images, see Fig. 4. *OCT* optical coherence tomography, *LP* lumbar puncture, *CSF* cerebrospinal fluid

have been employed to evaluate the optic nerve damage in chronic IIH [122–124].

B-mode *ocular ultrasonography* can be useful to exclude a condition of pseudopapilloedema, maybe due to the presence of drusen of the ONH, and to measure the optic nerve sheath diameter (ONSD). In a recent study, ONSD has proved to be enlarged more than 5.8 mm in patients with IIH (81% sensitivity, 80% specificity) and to decrease after therapeutic LP [125]. However, a precise cut-off value for ONSD has not be clearly defined [126–128] and binocular

measurements should be obtained, considering a possible asymmetry [129]. Color-doppler imaging may be also useful to detect an increase of peak systolic velocity of the central retinal artery, due to its location inside the optic nerve, in patients with IIH [125].

When diagnostic doubt persists in discriminating between papilloedema and pseudopapilloedema, fundus *fluorescein angiography can* be useful, showing a progressive increasing intensity and an area of fluorescence with fluorescein leakage from the oedematous disc in true disc swelling [75]. *Fundus autofluorescence* imaging, basing on the natural fluorescence properties of lipofuscin, may also reveal the presence of drusen of the ONH, as in some cases of pseudopapilloedema [130].

Diagnostic criteria

IIH diagnostic criteria have been firstly developed in 1937, based on Dandy's report of 22 patients who presented increased ICP, not due to mass lesions, and suggestive symptoms such as headache, fundus abnormalities, blurred vision and dizziness [131]. They originally included signs and symptoms of increased ICP (higher than 250 mmH_2O), no localizing signs except for 6th c.n. palsy, normal CSF composition and the absence of intracranial mass with normal or slit cerebral ventricles. Alongside the development of neuroimaging, a computed tomography or MR brain scan has been explicitly introduced in IIH diagnostic criteria ("modified Dandy criteria"), to exclude venous sinus thrombosis and other structural lesions. Similarly, the need to exclude possible secondary causes of increased intracranial hypertension has been emphasized [132, 133].

In 2013, Friedman and coworkers revised IIH diagnostic criteria, bringing back the term "*Pseudotumor cerebri* syndrome" and introducing the concept of "probable" diagnosis when all criteria (papilloedema or 6th c.n. palsy, a normal neurological examination except for c.n. abnormalities, a normal CSF composition, normal neuroimaging) are present with the exception of an increased CSF_{op} higher than 250 mmH_2O [70] (Table 3). Additionally, criteria for IIHWOP have been specifically described for the first time, pointing out that 6th c.n. palsy can be considered as an equivalent to papilloedema. When both are lacking, neuroradiological findings (empty sella, posterior flattening of the eyeball, distension of the perioptic subarachnoid spaces with or without optic nerve tortuosity, transverse sinus stenosis) become significant not only to exclude other underlying conditions, but to suggest the diagnosis. Indeed, a 64% sensitivity and a 100% specificity have been established for a combination of any three of four MR criteria for the diagnosis of IIH and the same MR criteria were suggestive of IIHWOP in 30% of patients with chronic headache and elevated opening pressure [81]. Since these last criteria have not been universally accepted, another update of the aforementioned "modified Dandy criteria" has been proposed by Wall and coworkers and applied in the IIHTT [63]. According to this revision, a definite diagnosis can be made even when CSF_{op} ranges between 200 and 250 mmH_2O, if one of the following additional criteria is satisfied: pulse synchronous tinnitus, 6th c.n. palsy, Frisén grade II papilloedema, exclusion of pseudopapilloedema by echography, evidence of transverse sinus stenosis by MR-venography, partial empty sella and distension of the perioptic subarachnoid spaces [134].

Since headache is the most common presenting symptom, diagnostic criteria for headache attributed to IIH were introduced in the ICHD by the Headache Classification Committee of the IHS in 1988 [135]. In the latest version (ICHD-3 beta) [61], the close temporal relation between a new-onset headache or a significant worsening of a pre-existing one and IIH is an important requirement to define a secondary headache attributed to IIH, regardless of whether its characteristics meet the criteria for primary headaches. It also implies that the development or changes in headache features occur along with CSF_{op} variations and that a reduction of CSF_{op} values results in the improvement of the symptom. As in Friedman's revised diagnostic criteria [70], the diagnosis of IIH in adults requires both a CSF_{op} exceeding 250 mmH_2O and the absence of altered CSF composition, with the presence of papilloedema as a support element to establish a causal relation between headache and IIH. Headache characteristics are not detailed in the last version of ICHD criteria, which shows greater applicability and sensitivity (86%) compared with the previous version (60%), but decreased specificity (50% vs 86%) [136]. ICHD-3 beta version criteria of the IHS are shown in Table 3.

Management

Low-calorie diet

Since obesity has been recognized as a certain associated factor with IIH, a low-calorie diet has been recommended in all patients affected. In a prospective study, 25 overweight women with IIHWP have been put under a low-calorie diet for 3 months, with a consequent mean weight loss of 15.7 kg. They exhibited a mean decrease of ICP of 8 cmH_2O, with a significant reduction in headache impact test scores, optic disc elevation, nerve sheath diameter and peripapillary RNFL thickness. An improvement in transient visual obscurations, tinnitus and diplopia were reported in some cases. Moreover, these reductions persisted for 3 months after the patients stopped the diet [137]. Bariatric surgery, inducing a major weight loss, seems to be more effective than low-calorie diet in reducing papilloedema and headache

Table 3 Latest updates of the diagnostic criteria for IIH and headache attributed to IIH

Diagnostic criteria for IIH Friedman et al. [70]
Required for diagnosis of pseudotumor cerebri syndrome
Definite diagnosis: the patient fulfills criteria A–E
Probable diagnosis: criteria A–D are met but the measured CSF pressure is lower than specified for a definite diagnosis
Papilledema
Normal neurologic examination except for cranial nerve abnormalities
Neuroimaging: normal brain parenchyma without evidence of hydrocephalus, mass, or structural lesion and no abnormal meningeal enhancement on MR, with and without gd, for typical patients (female and obese), and MR, with and without gd, and MR venography for others; if MR is unavailable or contraindicated, contrast-enhanced CT may be used
Normal CSF composition
Elevated LP opening pressure (≥ 250 mm CSF in adults and ≥ 280 mm CSF in children [250 mm CSF if the child is not sedated and not obese]) in a properly performed LP
Diagnosis of *Pseudotumor cerebri* syndrome without papilledema
Presence of criteria B–E for IIH plus unilateral or bilateral abducens nerve palsy
Suggestion of possible IIHWOP if criteria B–E for IIH are met plus 3 of the following neuroimaging criteria:
Empty sella
Flattening of the posterior aspect of the globe
Distention of the perioptic subarachnoid space with or without a tortuous optic nerve
Transverse venous sinus stenosis
Diagnostic criteria for headache attributed to IIH
Headache classification committee of the international headache society
ICHD-3 beta, 2013 [61]
New headache, or a significant worsening of a pre-existing headache, fulfilling criterion C
Intracranial hypertension has been diagnosed, with both of the following:
CSF pressure exceeds 250 mmH_2O (or 280 mmH_2O in obese children);
Normal CSF composition
Evidence of causation demonstrated by at least two of the following:
Headache has developed in temporal relation to the intracranial hypertension or led to its discovery
Headache is relieved by reducing the intracranial hypertension;
Papilledema
Not better accounted for by another ICHD-3 beta diagnosis

CSF cerebrospinal fluid, *CT* computed tomography, *MR* magnetic resonance, *LP* lumbar puncture, *IIH* idiopathic intracranial hypertension, *IIHWOP* idiopathic intracranial hypertension without papilloedema, *ICHD* International Classification of Headache Disorders

symptoms in obese patients [138] and has been judged as more cost-effective and safer than surgical CSF diversion [139]. It is notable that weight loss currently represents the only disease-modifying treatment for IIH [33].

Pharmacological treatment

In non-overweight patients or in those with more severe symptoms which do not resolve spontaneously, a low-calorie diet alone is not sufficient and a pharmacological management is required, considering the relief of symptoms and the preservation of visual function as the main goal. ACZ, a potent enzyme inhibitor of carbonic anhydrase, is still the main drug employed in IIH, since it is able to reduce CSF secretion at choroid plexus. Its efficacy has recently been evaluated in the IIHTT, a multicenter, randomized, double-masked, placebo-controlled trial [140]. ACZ has been administered at an initial dosage of 500 mg twice a day and increased to a maximum of 4 g daily, combined with a low-sodium low-calorie diet. In patients with IIH and mild visual loss, this treatment has proved to be more effective than diet alone in improving visual field function and quality of life measures and in decreasing papilloedema grade, though the extent of improvement was modest [140]. In another randomized placebo-controlled trial, no strong evidence was obtained about the efficacy of ACZ, maybe due to the small simple size, and a high discontinuation rate due to side effects was recorded [141]. Accordingly, despite modest positive effects were detected in patients treated with ACZ in the aforementioned studies, the Cochrane systematic review published in 2015 concluded that "there is insufficient evidence to recommend or reject the efficacy

of this intervention" [142]. An optimal dose has not been established, though the most commonly starting dose is 250–500 mg twice a day [33], generally slowly increased up to 1–2 g daily. The maximum dose of 4 g daily administered in IIHTT was scarcely tolerated due to side effects [143]. In ACZ-resistant headache, topiramate has been used as associated drug or as monotherapy. It is an inhibitor of voltage-gated sodium and calcium channels, increases GABA-induced chloride flux and inhibits glutamate-related neurotransmission, but it also exerts an action as mild carbonic anhydrase inhibitor. Used at a daily dose range of 100–150 mg, its efficacy has proved to be equal to ACZ at a daily dosage of 1000–1500 mg, with the added value of a major weight loss. Moreover, being a first-line agent for migraine prevention, topiramate may have a major benefit for those patients with IIH who suffer from migraine-like headaches [66, 144]. Both the drugs show similar undesirable effects, such as distal paraesthesia, hyporexia, tinnitus, dysgeusia, nephrolithiasis, vomit, nausea and diarrhoea. Few cases of severe metabolic acidosis with respiratory complications have also been described under treatment with ACZ [145].

Other drugs have been proposed for IIH treatment in case of contraindication or intolerance to ACZ or in combined therapies, such as furosemide, which has proved to reduce CSF secretion in animal models [146]. Octreotide, a somatostatin analogue blocking the human growth hormone receptor which is highly expressed in arachnoid villi and choroid plexus, has been proved to be effective in reducing pCSF and symptoms in a small-sample study [147].

Symptomatic therapies for headache management, especially migraine therapies, can be successfully used and recommended in patients with IIH suffering from headache with migraine features, for both the management of acute and chronic conditions. However, drugs determining weight gain and depression should be preferably avoided when choosing therapies for migraine prophylaxis [55].

Lumbar puncture and surgical treatment

Pharmacological treatment may fail or be poorly tolerated or even be inadequate to treat rapid-development symptoms. Non-medical interventions include LP and surgical procedures. LP may have a therapeutic role in addition to its diagnostic one in rapid-development cases of IIH to preserve visual function (Figs. 4, 5). In these cases, indeed, LP may serve as bridge-therapy standing by for surgical diversion. Cases of complete remission after a single LP have also been described [45], since a lowering of just 20–30 ml CSF seems to be sufficient to reopen the collapsed transverse sinus, reducing cerebral venous pressure which may alter CSF circulation. Surgical procedures include CSF shunts [46], transverse sinus stenting [44, 148] and the optic nerve sheath fenestration (ONSF) [149]. Unfortunately, they are not as effective in headache management as they are in the improvement of visual symptoms, so they should not be performed in patients with IIH and headache alone [33]. ONSF is preferred when patients mainly exhibit visual symptoms, especially if unilateral, with no or mild headache. The incision of the meninges encompassing the optic nerve, decreasing the pressure exerted on the nerve by the subarachnoid space, is effective in reducing papilloedema grade and improving visual field function in both eyes, even if unilaterally performed [149]. Though, it seems that a second surgery may be required in about 15% of cases and that over a third of patients have to undergo a subsequent CSF diversion [150]. Surgical CSF diversion may employ ventriculo-atrial (VA), ventriculo-peritoneal (VP) and lumbo-peritoneal (LPE) shunts. Both VP and LPE seem to be equally effective in decreasing symptoms, even if VP shunts have a major failure rate compared to LPE ones, but a minor need to undergo successive revisions [46]. Complications include shunt obstruction or infection, CSF leaks, rarely cerebellar tonsillar herniation, subdural and subarachnoid haemorrhages [66].

ONSF and CSF shunts seemed to be equally efficacious on visual outcomes in comparative case-series of 33 treated patients [151]. Preferentially, the current orientation consists in performing ONSF in case of severe papilloedema and considering CSF shunt when headache symptoms are prevalent, even if headache continues in until 68% of patients in post-operative 6-month follow-up and 79% at 2 years. Furthermore, a post-operative low-pressure headache can occur in 28% of cases [152]. Accordingly, surgical CSF diversion is not recommended to manage isolated headache symptoms [33, 102, 153].

A clinical trial is currently ongoing, with the purpose of comparing the efficacy of VP shunt, ONSF and medical therapy in patients with IIH and moderate-to-severe visual impairment [154].

Since BTSS has been proved to be a suggestive neuroradiological sign for IIH, the endovascular management through a stent placement may be considered as an option in patients who have failed standard therapy. Transverse sinus stenting can reduce ICP by increasing CSF drainage at the arachnoid granulations [44, 148]. In a study by Teleb and coworkers, symptom improvement after stenting has been reported in 94% of patients, reducing headache and papilloedema. The procedure has been performed at a not univocally defined gradient threshold, ranging from 4 to 10 mm Hg, in patients put under dual antiplatelet therapy [155]. Evidence of transverse sinus stenting efficacy on ICP decrease and visual symptoms has been provided by several more recent studies [40, 41, 156]. Despite the presence of a BTSS, unilateral stenting seems to be sufficient to determine a decrease of pressure gradient and resolution of symptoms,

even if clear recommendations are not available [157, 158]. Currently, isolated headache does not represent an indication to perform sinus stenting, due to the paucity of evidence [33, 102, 153]. Venous sinus perforation, stent migration, in-stent thrombosis, subdural haemorrhages and the development of recurrent stenoses proximal to the stent could represent rare but severe complications, while a short-lived ipsilateral headache can occur more often. The opportunity to guide the procedure of stent placement with intravascular ultrasound is currently being tested [159]. Main conservative, pharmacological and surgical treatments are summarized in Table 4.

The aforementioned surgical procedures have been evaluated in a systematic review including 41 studies and a total of 728 patients [160]. According to Kalyvas and coworkers, sinus stenting should probably represent the first-line modality of surgical treatment whenever BTSS with a high-pressure gradient is documented, regardless of the clinical presentation.

If such a condition does not occur or if stenting has failed, ONSF should be considered in patients with visual symptoms and no headache, due to its high efficacy and minor cost, while CSF shunt could be taken into account later if severe headache develops or in patients exhibiting headache as the only or prevalent symptom [160].

Prognosis and follow-up

IIH can be a challenging condition, occurring with changeable course and prognosis and requiring a prompt diagnosis and treatment. In case of rapid progression of symptoms, preserving visual function is the main aim and a non-pharmacological approach is often necessary. It is not accident that the term "benign" is no more employed to define this clinical condition, since permanent visual loss can occur in up to 10% of cases, mostly in men [65].

Table 4 Management of IIH

Management of IIH		
Conservative	Pharmacological	Surgical
Low-calorie diet	ACZ	Bariatric surgery
	Topiramate	LP
	Furosemide	TSS
	Octreotide (poor evidence)	ONSF
		CSF diversion (VA, VP or LPE shunts)

ACZ acetazolamide, *LP* lumbar puncture, *TSS* transverse sinus stenting, *ONSF* optic nerve sheath fenestration, *CSF* cerebrospinal fluid, *VA* ventriculo-atrial, *VP* ventriculo-peritoneal, *LPE* lumbo-peritoneal

Furthermore, patients diagnosed and treated may relapse years later, often after a weight gain [8]. Relapses may also occur during pregnancy, especially during the first two trimesters, with similar clinical outcomes compared with that one of non-pregnant women, but possibly requiring different therapeutic strategies [161–163].

In a retrospective observational study evaluating long-term outcomes in IIH patients with different ages at diagnosis, recurrences mainly occurred within 3 years from treatment discontinuation in adolescents and adult patients and within 1 year in prepuberal children, regardless of CSF_{op} and obesity. Moreover, optic neuropathy and consequent visual decline was prevalent in adult-onset IIH [164]. The earliness of diagnosis, established within 6 months from symptom onset, seems to be a positive prognostic factor for visual improvement [165]. Moreover, the severity of visual defects at onset has proved to correlate well with the final visual outcome [166] and to influence the recurrence rate, which has reported to be greater in women with previous multiple pregnancies in one study [167].

Therefore, monitoring is mandatory in patients with IIH, particularly referring to IIHWP, and should include the assessment of visual acuity, pupil examination, visual field, fundus oculi and BMI [33]. At least an annual optometric assessment should be performed, with OCT as an adjunctive useful tool to monitor the damage of the macular RNFL over time and to detect recurrences [117].

A risk stratification has been recently proposed to provide appropriate monitoring, mainly based on visual status [168]. Fundoscopy and visual field assessment should be assessed at increasingly short intervals ranging from 3 to 6 months for patients at low risk, who do not exhibit either papilloedema or visual impairment or abducens palsy, to 1–4 weeks for high-risk patients with rapidly evolving visual impairment or moderate/severe papilloedema at onset, eventually supported by a MR with orbits scan.

For patients with IIHWOP, whose risk of vision loss seems to be minimal over time, visual monitoring is not needed for a long period and surgical procedures are not recommended [33, 102]. Conversely, in this group of patients as well as in all patients with IIH, weight loss should be pursued if appropriate and headache monitoring in terms of frequency and severity could be useful and achieved with the support of a headache diary. The eventual persistence of headache symptoms even after the lowering of ICP has to be considered and treated as appropriate, not least to avoid the development of medication-overuse headache, which affects about 37% of patients with IIH [102].

Finally, a multidisciplinary approach with the involvement of neurologists, neurosurgeons and ophthalmologists is required to the management of IIH, along with further studies to explain the still unknown underlying pathogenesis.

Conclusions

The aim of this review is to focus on what is known about IIH and what is currently gaining importance in the knowledge and management of a condition which is still only partially understood. Particularly, most of the recent studies reflect increasing interest in the identification of IIHWOP. Indeed, these patients usually suffer from chronic headache and are long-term treated with a symptomatic of prophylactic therapy for a "primary" disorder, instead of being treated for a "secondary" headache, thus removing the underlying cause. Therefore, physicians, and foremost neurologists, should be able to suspect IIH even when faced with a multiform condition (see Table 2). Once the assumption of IIH has been made, neuroradiological signs can help to suggest the diagnosis. However, CSF_{op} remains an essential criterium to make "definite" a probable diagnosis of IIH. A longer pCSF monitoring, though, may allow to identify patients with increased mean ICP and abnormal pressure pulses even when the instantaneous detection of pCSF values may be misleading due to its variability. The employment of these and other additional examinations, as OCT, VEPs, ocular ultrasonography, autofluorescence and fluorescein angiography, reflects the willing to increase diagnostic accuracy and to correctly identify patients who could be easily misdiagnosed. On the other hand, since the concept of IIH has been extended to involve cases of IIHWOP mainly characterized by chronic headache, the risk of overdiagnosis should also be taken into account [103]. A lot still needs to be understood and it is not excluded that, as for other conditions before, what is currently named as "idiopathic" will not be defined like that any longer when the precise physiopathological mechanisms will be understood.

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