IDIOPATHIC INTRACRANIAL HYPERTENSION: UPDATE ON THE PATHOGENESIS, CLINICAL FEATURES AND THERAPY

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Summary

Idiopathic intracranial hypertension (IMS) is a syndrome of unknown etiology characterized by increased intracranial pressure in the absence of an intracranial mass. The annual incidence of IMS in the general population ranges from 0.03 to 1.56 cases per 100,000 and reaches up to 19 cases per 100,000 for young obese women. The pathophysiology of the disease is quite complex and not yet fully elucidated. The main theories support the reduced absorption of cerebrospinal fluid (CSF), the increased intracranial venous pressure, blood hypercoagulability and hormonal disorders. The clinical features include headache, visual disturbances, nausea, vomiting, tinnitus and photophobia. The modern therapeutic approach involves diet and lifestyle changes, medication, lumbar puncture, surgical diversion of CSF, decompression of the optic nerve, bariatric surgery and stent placement to the venous sinuses. In this review we describe the aforementioned condition emphasizing in the risk factors, clinical features and therapy including the latest data that currently exist in literature.

Keywords: idiopathic intracranial hypertension, obesity, headache, papilledema

Introduction

Benign or idiopathic intracranial hypertension(IIH), formerly known as pseudotumor cerebri, is a syndrome of unknown etiology that is associated with increased intracranial pressure in the absence of radiologic findings of an intracranial mass.

It was described for the first time in 1893 by the German physician Heinrich Quincke[1] under the name serous meningitis, but the term pseudotumor cerebri was introduced in 1904 by Max Nonne, also German physician. The first important study on IIH was published in 1937 by the great and pioneer American neurosurgeon Walter Dandy[2], who described the clinical course of 22 patients with IIH in 7-year follow-up period. All of the patients presented with symptoms of increased intracranial pressure: headache, blurring of vision and vomiting. In fundoscopy, there was papilledema and in some cases retinal hemorrhages, probably caused by the long-standing intracranial hypertension. In these patients, Dandy performed subtemporal craniectomy with impressive results. That time, he

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had attributed the increase in intracranial pressure to hemodynamic changes in the vascular network of the brain. IIH is an exclusion diagnosis that requires a thorough examination of the patient's central nervous system. The criteria for the diagnosis of IIH were first introduced by Dandy in 1937 and since then they have been modified over time by many scientific groups. However, the Friedman and Jacobson[3] Criteria(Table 1), defined in 2002, are those that are worldwide accepted and used today.

TABLE 1. Friedman and Jaccson criteria for IIH
1. If symptoms present, they may reflect those of generalized intracranial hypertension or papilledema.
2. If signs present, they may only reflect those of generalized intracranial hypertension or papilledema.
3. Documented elevated intracranial hypertension measured in the lateral decubitus position.
4. Normal cerebrospinal fluid composition.
5. No evidence of hydrocephalus, mass, structural or vascular region on magnetic resonance imaging (MRI) or contrast-enhanced computed tomography for typical patients, and MRI or MR venography for all others.
6. No other cause of intracranial hypertension identified.

Although a rare disease entity, IIH has evolved lately into an object of intensive medical research, mainly due to the increasing prevalence of obesity. Indeed, it was recently published that the annual health expenditures for IIH in the United States exceed 440 million dollars, due to the frequent admissions to the hospital, the ambivalent therapeutic measures and lost productivity of younger population.4 Since the incidence of obesity is constantly rising, the number of patients with IIH and the relative expenses are about to increase even more in the following years. In this review we describe the aforementioned condition, emphasizing in the risk factors, clinical features and therapy including the latest data that currently exist in literature.

Epidemiology

The annual incidence of IIH, as far as the United States are concerned, is 0,9 cases per 100.00 in Iowa and 1,07 cases per 100.000 in Louisiana, according to Durcan5. These numbers increase to 19 new cases per 100.000 every year in women 20-44 years old that are 20% above their ideal weight. Moreover, in a retrospective study6 that was performed in Sheffield in United Kingdom, the annual incidence and prevalence of the disease were found to be 1,56 and 10,9 cases per 100.000 respectively for the general population. In obese women the numbers are 11.9 and 85, 7 cases per 100,000. The

reported ratio of IIH between men and women ranges from 4:1 to 15:1. 2,7-10 Bruce et al recently showed in a large number of cases that only 10% of patients are men, who in one hand have the same Body Mass Index(BMI) as the affected women but on the other hand are about 10 years older when diagnosed[11]. The frequency of obesity in patients with IIH is approximately 71-94%.[7,10,12-13] In a prospective study of 50 patients by Wall and George[14, 47](94%) were obese and in the last 12 months before the onset of symptoms there was an average weight gain by 7,7 kg. The mean age of disease's onset is reported to be 28 to 35 years. [7,10,13-14] IIH may also appear in younger patients, however it is rare in prepubertal age and it seems that obese girls are not affected more frequently.[15] IIH appears to have a higher incidence in the Western World compared to Asia[16](1/100,000 vs 0.03/100,00017) although no relation to patient's ethnicity has been proven so far. Nationality seems to affect the prognosis of visual disturbances; worse in Blacks compared to Whites living in America(RR=3,5)[18] and worse in white American compared to white French patients(RR=8,7)[19]. Finally, it hasn't yet been clarified whether there is genetic background or not˙ however familial cases have been occasionally reported.

Risk Factors

1) Obesity: Idiopathic intracranial hypertension as highlighted above primarily affects obese women of childbearing age. A recent multicenter case-control study compared cases of newly diagnosed women with IIH to women with other neuro-ophthalmological problems and showed that there is a proportional relationship between the risk of developing IIH and larger BMI.[20] The same survey also showed that even non-obese patients, i.e BMI <30, are at increased risk for IMS if they had recently moderate increase in body weight (5-15%). Another study[21] examined a sample of 26 women with recurrent IIH and found that their BMI was higher during the relapses of the disease compared to the one they had durng the initial diagnosis. A comparison was performed between this sample and a group of 24 women with diagnosed but non-relapsing IIH and it was found that women without recurrences had constant weight, while patients with relapses had a 6% gain in their weight. Therefore, even small increases in weight can raise the risk for IIH recurrence. A survey from Israel[22] also suggested that female fat distribution, i.e in buttocks and thighs, is more correlated to IIH than central-visceral obesity, which is undoubtedly associated with cardiovascular disease and diabetes.

2) Medication: Many drugs have been reported to be involved in the pathogenesis of IIH. Those that are most commonly implicated are tetracyclines, especially minocycline [23,24] and doxycycline[25], per os retinoids given for skin diseases[26] (acne, etc.), retinoic acid given for acute myeloid leukemia[27](M3-promyelocytic), per os contraceptives and the abrupt withdrawal of corticosteroids[28,29]. However, prospective studies have failed to confirm these possible associations.[5,30,31] Especially for oral contraceptives, newer data suggest that there is no statistically significant increase in the incidence of the disease in wom-

en taking the pill compared to the general population.[5,32]
3) Vitamin A: The fat-soluble vitamin A (retinol) alters the structure and composition of the arachnoid granulations. Investigations in animals deficient of vitamin A showed that they had an increased pressure in the CSF, although the mechanism is still uncertain.[33] There have also been reported cases of infants with vitamin A deficiency and intracranial hypertension, which subsided when the appropriate treatment was administered.[34] The excessive intake of the vitamin might also contribute to the development of the disease. [35,36] In two studies of patients with IIH, retinol levels were measured in CSF and were found to be elevated. [37,38] Furthermore, one of these studies showed that the levels of retinol binding protein (RBP) in serum were elevated, whereas in CSF were lower than normal. A large study that is currently conducted in the U.S and involves measurements of vitamin A in patients with IIH, is expected to elucidate more on that particular subject.
4) Pregnancy: Pregnancy has been traditionally associated with increased likelihood of occurrence of idiopathic intracranial hypertension. The literature data are conflicting. There are several studies that support this view, attributing to the disease a mean prevalence of 1 in 870 live births. [39,40] However, the study of Ireland et al32 rejects the higher incidence of the disease during pregnancy, although the small number of its sample questions the validity of the results.
5) Other diseases: IIH has been associated with various diseases over time. In a portion of 14-32%[10,12,14,32] of patients, arterial hypertension has been reported and in one study blood pressure was significantly higher in patients with IIH compared to controls.[32] It remains unclear, however whether this association is real and does not reflect the higher blood pressure levels of obese people, which are more frequently affected by the disease. Obstructive sleep apnea[41] has been implicated as well and it might be associated with worse prognosis, although it has not yet been established whether it is an independent risk factor or obesity is the common pathophysiological substrate. Other concomitant diseases occasionally reported include diabetes, SLE, sickle cell anemia, chronic migraine, thyroid disease, clotting disorders, cystinosis, ulcerative colitis, hypoparathyroidism, primary and secondary hyperaldosteronism etc. [5,10,14,42,43] On most cases we do not know if this relationship is accidental, due to undiagnosed venous sinus thrombosis or random coexistence.
6) Menstrual Irregularities: According to studies, menstrual cycle disturbances are a more common finding in women with IIH compared to other women and constitute a frequently reported symptom. In a questionnaire given to 40 patients with IIH, menstrual cycle changes just before the diagnosis of IIH were more frequently reported opposed to the 39 controls.[32] The same study demonstrated that menarche in the age of 13 years old and earlier was more likely in women with disease. Polycystic ovarian syndrome also appears to coexist with IIH at a high frequency, since 44% of women with PCOS are obese.[44,45] Menarche[46], oligorrhea and amenorrhea[47] have also preceded the onset of symptoms according to several reports. However, there is no published evidence of hormonal dysfunction to specify these findings and could therefore be attributed to obesity on the majority of cases.

Pathogenesis

Several theories have been developed regarding the pathophysiological structure of idiopathic intracranial hypertension but it's still not fully elucidated. We will mention below the most important ones.

• ***Impaired CSF absorption***

An earlier theory suggests that IIH is secondary to decreased absorption of CSF. Studies conducted in the 90s used various techniques such as intrathecal injection of saline and cisternography with radioisotopes in patients with IIH and observed resistance to CSF absorption and delayed circulation.[48-52] Therefore, impaired CSF flow could be a possible mechanism for developing the disease

• ***Elevated intracranial venous pressure***

Literature data are conflicting whether the increased pressure in the venous sinuses is the cause or the result of increased intracranial pressure,[53-55] although according to a proposed model, it seems that the two processes reinforce one another. From venographies that were carried out in several series of patients,a significant degree of stenosis in one or both transverse sinuses was found in the absence of an occlusive thrombus.[56-58] The hypothesis that transverse sinus stenosis (TSS) and IIH are pathologically connected is by the fact that in a large portion of patients susbstantial reduction in intracranial pressure and symptoms relief were noticed after stent placement in the narrowed transverse sinus.[54,55,59] It is also controversial whether the TSS is reversed by CSF diversion surgery, since both resolution and persistence of the narrowing after surgery have been described in literature.[54,55,60-62] Karahalios et al[63] described 5 patients with IIH, who had increased pressure but normal anatomy of venous sinuses and increased pressure in the right atrium, leading to the conclusion that venous hypertension is the Our study suggests that elevated intracranial venous pressure may be a universal mechanism in IIH of different etiologies.Thus, researchers have turned their interest to the part of TSS in IIH and whether it precedes or follows the onset of the disease, although there are published cases where stenoses were an incidental finding due to anatomical variations, i.e septa, large arachnoid granulations or trabeculae.[64,65]

• ***Hypercoagulability***

Another proposed mechanism for the increased intracranial pressure is microthrombi formation within the cerebral veins due to increased blood coagulability, disrupting in this way the normal absorption of CSF.[66-73] Many researchers argue that the presence of thrombophilia excludes by definition the diagnosis of IIH, but the existence of a statistically important coexistence of IIH and thrombophilic disorders should be taken seriously into consideration. At present however, blood clotting tests are not recommended to all patients with IIH unless there radiologiv demonstration of a venous thrombus or a positive personal-family history of thrombophilia.

• ***Hormonal Dysfunction***

Observations on the possible role of vitamin A in the pathogenesis of IIH have led to emerging research interest in the endocrinal effects of adipose cells as a hormonally active tissue.[74,75] Both leptin and retinol binding protein (RBP), which acts as a regulator of the cells sensitivity to insulin, are secreted by adipocytes and according to theories may be involved in the pathophysiology of IIH.[76-77]

Laboratory and Imaging tests

According to the Friedman and Jacobson Criteria[3], radiologic investigation for IIH should be normal, which means that the existence of a mass lesion responsible for the increased intracranial pressure and thrombosis of venous sinuses must be excluded. For this reason, magnetic resonance imaging (MRI) should always be carried out in patients suspected for IIH and it can be accompanied by CT(CTV) or magnetic resonance venography (MRV).

Moreover, CSF examination should be free of cytological and biochemical abnormalities, while opening pressure should be over 200 mmH2O in non obese and over 250 mmH2O in obese patients measured with lumbar puncture in lateral decubitus position.

Today, with the assist of advanced and more accurate imaging methods, various radiologic findings[78-85] have been reported to be associated with the disease while but are neither sensitive nor specific for it and can also be observed in normal subjects. These findings are summarized in Table 2.

TABLE 2. Imaging finding in patients with IIH
• Optic nerve sheath distention and tortuosity
• flattening of the posterior pole of the eye
• Stenosis of one or both tranverse venous sinuses
• Empty sella turcica
• Foramen ovale widening
• Optic nerve enhancement after lamina cribrosa
• Cavernous sinus and Meckel's cave narrowing

Uttam's study[86] claims that remission of the above findings after CSF drainage not only confirms the diagnosis of IIH but also proves the response to treatment. It also recognizes the important role of MRI in monitoring and evaluating the progress of patients in order to avoid repeated LPs for the measurement of CSF pressure.

A new, promising approach to IIH is the molecular study of metabolites (metabolomics) in CSF.[87,88] This will enable us to identify potential markers involved in the pathophysiology of the disease, to rule out other neurological diseases with similar clinical features and create new areas of research.

Clinical Manifestations

The most common symptom which patients with IIH complain for is headache, at a rate up to 98%[7,12,14] and it's the main reason for seeking medical care. In 2004 the International Headache Society(IHS) classified the diagnostic criteria for headache due to IIH(Table 3). The characteristics of headache varies from patient to patient, but according to most retrospective studies it is more intense in the morning, sometimes making patients to wake up and annoys them on a daily basis. Also, the headache[89] often progressively increases in

intensity, can be either localized(occipital, retrobulbar) or affect the whole skull and has a pulsatile character in over 80% of patients. It can mimic migraine and tension headache or change by maneuvers that increase jugular venous pressure and therefore the intracranial pressure such as coughing and Valsalva's maneuver.

TABLE 3: IHS criteria for headache due to IIH (2004)

A. Progressive headache with at least one of the following characteristics and fulfilling critera C and D:
    1. daily occurccence
    2. diffuse and/or constant (non-pulsating) pain
    3. aggravated by coughing or straining
B. Intracranial hypertension fulfilling the following criteria:
    1. alert patient with neurological examination that either isnormal or demonstrates any of the following adbnormalities:
        a. papilledema
        b. enlarged blind spot
        c. visual field defect (progressive if untreated)
        d. sixth nerve palsy
    2. Increased CSF pressure (>200 mm H_2O in the non-obese, >250 mm H_2O in the obese) measured by lumbar puncture in th recumbent position or by epidural or intraventricular pressure monitoring
    3. Normal CSF chemistry (low CSF protein is acceptable) and cellularity
    4. Intracranial diseases (including venous sinus thrombosis) ruled out by appropriate investigations
    5. No metabolic, toxic or hormonal cause of intracranial hypertension
C. Headache develops in close temporal relation to increased intracranial pressure
D. Headache improves after withdrawal of CSF to reduce pressure to 120-170 mm H2O and resolves within 72 hours of pesistent normalisation of intracranial pressure

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Visual disturbances are the second most common symptom of patients with IIH and it's considered to be secondary to chronic papilledema. Most often they involve transient obscurations in 57-72%[7,1,14] of patients, which are described as shadows or black spots in one or both eyes lasting a few seconds to minutes. Rarely patients might present with diplopia, photopsia and loss of vision, especially peripheral. Papilledema is a universal clinical finding in patients with IIH and hence its absence should make the diagnosis questionable. Nonetheless, there have been a few reported cases of patients with headache and increased CSF pressure without papilledema.[90-92] A follow-up on a regular basis by an ophthalmologist is necessary for patients with IIH, because the chronic swelling will eventually lead to optic nerve atrophy and permanent vision loss. It's usually symmetrical, but in 10% it may also be asymmetrical or unilateral. Mild swelling of the optic disc might be difficult to detect with conventional funduscopy and therefore a slit lamp examination or fluorescein angiography should be used. It's also necessary to examine the visual fields. Wall's study[14] showed deficits in perimetry of Goldmann in 96% of eyes examined and automated perimetry of Humphrey in 92%. The constriction of peripheral vision is often arcuate involving the nasal (particularly lower-nasal) visual fields. It is worth mentioning that there is no correlation between the severity of papilledema and the degree of visual field loss. The central vision and visual acuity are affected only

in advanced stages of the disease.[93]

Horizontal diplopia might be found in 1/3 of patient, paresis of the abducens nerve(VI), either unilateral or bilateral in a 10-20% (probably because of its long course within the subarachnoid space) and in some cases facial(VII) paresis.

Finally, a percentage of patients, as much as 60%[14], complains of pulsatile tinnitus describing the annoying noises as "whooshing" or "roaring". Rare cases have reported symptoms of meningism[3](nausea, vomiting, photophobia) and pain located in the neck, shoulder or radicular pain.

Differential diagnosis

The clinical features of IIH vary from patient to patient and are not specific for the disease. The differential diagnosis will mainly include other diseases which increase the intracranial pressure and cause papilloedema:
1.   Cerebral venous hypertension:
•   Obstruction of the upper sagittal or transverse sinus, which may be due to
i.   Hypercoagulability (cancer, oral contraceptives, dehydration, antiphospholipid
     syndrome, etc.)
ii.   Injury
iii.   Postoperative complications (eg after radical lymphadenectomy)
iv.   Various infections
v.   Postpartum thrombosis
•   High flow arteriovenous(AV) malformation, where there is increased blood volume
2.   Arachnoid adhesions due to meningitis (tuberculous, fungal, sarcoidosis, etc.)
3.   Obstructive hydrocephalus (mass lesion, Sylvius' aqueduct narrowing, etc.)
4.   Diseases that increase the concentration of protein in CSF (SLE, Guillain-Barre' syndrome)
5.   Metabolic disorder

Treatment

The goal of the treatment is remission of symptoms and preservation of vision. IIH is a chronic disease and therefore long-term careful monitoring of patients is mandatory irrespective of the therapeutic method implemented. First of all, a very thorough history must be obtained in order to identify any predisposing factors, such as drugs, obstructive sleep apnea, etc., and select the appropriate treatment based on the severity of symptoms and signs. The main treatment options are the following:

Conservative Measures

Diet and lifestyle changes
Weight loss is the first directive given to all obese patients with IIH. Especially for those with mild symptoms, a diet low in salt, exercise and a weight loss program, even a modest amount of 5-10% of total body weight, seem to offer a considerable improvement in symptoms.[94-97] Despite that, most of

the time weight loss alone is not sufficient and thus medication should be initiated.

Medication

In patients with mild to moderate symptoms we prescribe medication in order to reduce CSF production and decrease intracranial pressure. Acetazolamide remains the mainstay of treatment, while alternative options include loop diuretics, topiramate and mannitol if acetazolamide is inadequate or poorly tolerated due to adverse effects.

Acetazolamide is a carbonic anhydrase inhibitor and reduces the production of CSF and intracranial pressure leading to a significant alleviation of signs and symptoms. [98-99] However, no trial data so far confirm its effectiveness. [100] Kessler and colleagues[12] followed-up 54 patients with IIH for a mean period of 6,2 years. During this period, 33 patients (61%) had multiple (≥ 2) relapses of the disease, but no relapses occurred while patients were treated with acetazolamide. Currently in the U.S a large, multicenter, randomized trial is conducted comparing weight loss and acetazolamide versus weight loss and placebo in patients with mild to moderate IIH.[101]

The loop diuretics most commonly used are furosemide and bumetanide. They are administered either alone or with acetazolamide when it's therapeutically insufficient. A case of a 13 year-old obese girl with IIH refractory to acetazolamide and furosemide was recently published, which showed complete remission of symptoms and papilledema when she was treated with bumetanide.[102] According to latest literature data, bumetanide, other than its action in renal tubules, it also prevents the increase in volume of astrocytes by inhibiting Na+ / K+ / Cl- co-transporter on their cell membrane.[103] Therefore, the effect on regulating glial volume may constitute an additional effective mechanism for the treatment of idiopathic intracranial hypertension .

Topiramate is an antiepileptic drug with weak carbonic anhydrase inhibitor activity. Often used in the treatment of migraines, it was recently approved for weight loss, making it an ideal choice for obese patients with headache as a prominent symptom.[104,105] According to a recent, small, randomized trial, it has about the same efficacy with acetazolamide for mild to moderate IIH.[106] Mannitol also has been used successfully in some patients with IIH.[107] However, both topiramate and mannitol are not always tolerated by patients, because of the excessive diuresis and mild cognitive dysfunction they can cause, and consequently caution in their use is required.

Steroids are no longer administered to reduce intracranial pressure, although previously they were given on a more frequent basis. Their use was gradually reduced for two reasons: first, they cause weight gain and secondly, abrupt discontinuation can lead to rebound intracranial hypertension. [108-110] Today, steroids can only be administered in high doses intravenously in fulminant forms of IIH, while patient waits for surgical intervention.[111,112]

Invasive Methods

Lumbar puncture

In a patient with clinical suspicion of idiopathic intracranial hypertension and after conducting Magnetic Resonance Imaging(MRI) to exclude intracranial mass, the next step is to perform a lumbar puncture(LP), which has both diagnostic and therapeutic role. Although most patients after the first LP report remission of their symptoms, this method usually provides transient improvement and relapses can become so frequent, that multiple punctures are required and a large volume of CSF might be removed (up to 30 ml). This causes the following problems: (1) it increases the risk of complications such as herniation, meningitis and subdural hematoma, (2) it's technically more difficult and time consuming to perform multiple LPs in obese patients, (3) the patient because of anxiety and headache after LP, from one point on ceases to be cooperative and (4) the replacement of CSF after the LP can be so rapid that several punctures in the same day must be performed to relieve symptoms.

Thus, multiple LPs are only performed during the acute onset or worsening of the symptoms, in cases of fulminant presentation and to reduce intracranial pressure until patient undergoes CSF diversion surgery.

It is worth mentioning that LP is the preferred treatment option in pregnant women with IIH,since many of the drugs prescribed for IIH are contraindicated during pregnancy, to avoid the risks of surgery and because of possible regression of the disease after delivery.[113]

Although IIH is generally self-limited ,a large percentage of patients, as much as 25%, will continue to have a deterioration of vision and persistent headaches,[110] despite medication and lumbar punctures. In these patients, the recommended solution is surgery including shunt placement in CSF to reduce intracranial pressure and alleviate headaches and surgical decompression of the optic nerve when the patient's vision is threatened. Recently, stent placement in the transverse sinuses and bariatric surgery in obese patients have become increasingly popular.

CSF diversion

Shunt placement is the most common neurosurgical procedure performed regarding IIH.[114] There are two options: ventriculo-peritoneal(VPS) and lumbar-peritoneal(LPS) shunt. In most patients with IIH, the ventricles are smaller in size compared to normal, making neurosurgeons to avoid placing a ventricular catheter and to prefer the second solution.[115] LPS compared to VPS is technically easier, accompanied by a lower rate of postoperative infections (1% vs. 7-15%), but has a higher failure rate (50% at 2 years for LPS compared to 20% at 2 years for VPS) making very often a surgery revision mandatory.[114] Probably the somatotype of obese patients with IIH accounts for the high failure rate of LPS. It should be noted that patients with IIH not uncommonly develop chronic headaches despite the decline of intracranial pressure to normal levels and thus the failure of one or the other method must be carefully evaluated each time and measurement of the intracranial pressure should be measured

before changing the shunt.116 Advanced techniques allow endoscopic assisted placement of ventricular catheter for slit-like ventricles. Finally, in cases where LPS or VPS cannot be performed there is the option of cistern magna shunting, which is nonetheless accompanied by a larger complication rate compared to the other two surgical procedures.[117]

The literature data on the effectiveness of CSF surgical diversion is ambiguous. As far as visual disturbances and papilledema are concerned, most studies show more than 95% visual stabilization to complete remission.[118-122] The results are not unfortunately as encouraging for the headache. According to one study[123], out of 42 patients who underwent catheter placement in CSF, almost all reported resolution of symptoms immediately after surgery, while 20% and 50% reported headache recurrence at 1 and 3 years postoperatively, respectively, despite normal intracranial pressure and functioning shunt.

Optic nerve sheath fenestration(ONSF)

During ONSF, ophthalmologists create slits in the optic nerve sheath to rapidly decompress papilledema and prevent deterioration of the patient's vision.[124-128] This procedure does not reduce intracranial pressure and therefore symptoms such as headache, nausea, vomiting and diplopia will not subside.[129-132] This means that conservative treatment and a neurosurgical CSF diversion are almost always necessary in these patients. Some physicians prefer this method for the group of patients presenting only with visual disturbances and no headache.

The mechanism by which the surgery relieves pressure on the optic nerve head and reverses papilledema is not yet fully clarified. Initially, during surgery a fistula is created between the subarachnoid space and the orbital cavity in order to drain the cerebrospinal fluid.[133] Postoperatively, the prevailing theory suggests that fibrous connective tissue is formed in the slits thereby preventing the transmission of high intracranial pressure through the subarachnoid space (which is part of the optic nerve sheath after the lamina cribrosa) to the optic apparatus.[133] It's also very interesting the fact that in 50% of patients who undergo surgical decompression of the optic nerve in one eye will have regression of the papilledema in the other eye.[129] This happens probably due to the connection of the sheaths of the two optic nerves in the optic chiasm.

Unlike surgical diversion of CSF, ONSF is performed only once in each eye and needs not to be repeated. It is quite safe, doesn't implement foreign objects in the eyeball (hence the possibility of infection is insignificant) and doesn't cause cosmetic problems thanks to the newer endoscopic transnasal approaches that do not require an external incision. Complications have been reported occasionally and include disorders of the pupil reflex if the optic nerve or the accompanying vessels are injured.[134-136]

Bariatric Surgery

The role of bariatric surgery in the treatment of IIH is not yet established. Undoubtedly it contributes to rapid and substantial weight loss by reducing in this way the intracranial pressure. This makes it a valuable tool for the management of patients with severe obesity. However, until today it cannot replace surgical diversion of CSF and ONSF, particularly in fulminant cases with severe vision deterioration.

So far in the literature, 12 studies class IV have been published with 66 patients with IIH who underwent bariatric surgery, mostly Roux-en-Y gastric bypass.[137-148] The average weight loss in these patients is 45,5 kg. Data on the postoperative condition of the patients and the effectiveness of the procedure are the following[149]: (1) 92% of patients reported significant to complete remission of symptoms, while the remaining 8% consists of patients with pulsatile tinnitus as the primary symptom and a patient who failed to lose weight with the procedure (2) 97% of patients with papilledema had complete resolve (3) The visual field defects were corrected in 92% of patients.

The above results are impressive but must be carefully assessed, firstly because they include only obese patients with IIH, secondly, the number of existing data is still small and third, most published studies are single case reports where surgery succeeded in resolution of symptoms and hence patients that failed to improve are not reported. We should also mention that the time to perform such a surgery requires careful planning because adhesions may follow and increase complication rate of a future CSF diversion surgery. Thus, a large randomized trial or a cohort study would be ideal to further elucidate the benefit/risk ratio of bariatric surgery in the treatment of IIH.

Dural venous sinus stent placement

As emphasized earlier, intracranial venous sinus stenosis is a frequent finding in angiography of patients with IIH[57,64,150] but it's still equivocal whether it's the cause or the result of increased intracranial pressure. Stenosis mainly occurs in the transverse sinus, near the junction with the sigmoid sinus, mostly unilaterally.[151] In many patients, the stenosis was reversed after performing LP or surgical CSF diversion.[61,64,150,152] Equally numerous are the literature reports of patients who underwent stent angioplasty within the transverse sinus with very satisfactory postoperative results.

In order to determine if a patient is candidate for stent placement, it's necessary to perform angiography (usually DSA or MRA) to find the narrowing and transverse sinus manometry across the stenosis. The latter requires femoral venous access to navigate the catheter and uses a standard pressure transducer to record the pressure difference between the proximal and distal end of the stenosis. Differential pressure greater than 10 mmHg is hemodynamically significant and associated with a higher chance of improving CSF circulation and interstitial edema decrease (due to venous congestion) after placing the stent. In a study with 10 patients in whom manometry showed differential pressure greater than 10 mmHg, all patients reported significant to complete resolution of symptoms after surgery, particularly headaches.[153]

The first stent placement in the transverse sinus for the treatment of IIH was attempted in 2002 by Higgins[154] in an obese woman with bilateral stenosis of the sinuses and intracranial hypertension refractory to any form of treatment. Currently in the literature 143 cases of venous sinus stent placement have been reported.[154-163] 87% of them are

women, the average age is 41,4 years old and the average BMI is 31,6 kg/m2. We further down present the improvement rates of symptoms in a mean follow-up period of 22, 3 months postoperatively: headache-88%, papilledema-97%, abnormal vision-87% and pulsatile tinnitus-93%.

Patients who are about to undergo stent placement must be administered 7-14 days before the procedure anti-platelet drugs to reduce the risk of sinus thrombosis after angioplasty. The drugs most commonly given are aspirin and clopidogrel and should be continued from 6 to 12 weeks postoperatively, aspirin sometimes for a lifetime. Temporarily after surgery the patient might experience frontal or temporal headache, due to distension of the meninges covering the transverse sinus.[156,157] Transient hearing loss, stent thrombosis, subdural hematoma and death to a patient have been reported.[161,163] Generally these complications are rare and the surgery is considered to be very safe, as long as it is performed by a specialized interventional neuroradiologist. Finally, in some cases recurrent stenoses proximally to the stent might occur, leading to increase of the intracranial pressure and reappearance of the symptoms.

Until there is a randomized clinical trial to evaluate its efficacy, this method should not be implicitly recommended to all patients with IIH, but only to those with radiologic and manometric evidence of stenosis that have failed to improve with conservative therapy and standard surgery.

Subtemporal craniectomy

This operation was the surgical gold standard treatment of IMS prior to the development of CSF diversion procedures. The first and largest study of patients who underwent subtemporal decompression was published by Dandy[2] in 1937. Of the 19 patients with surgically IIW, 14 were monitored postoperatively and all had complete resolution of papilledema, nobody had a second surgery and the postoperative mortality was 0%. In a more recent paper by Kessler[164], out of 8 patients treated with subtemporal decompression, all within one month of surgery showed significant improvement in their vision, while 5 required valve placement in the CSF to control the headaches.

Despite these remarkable results, subtemporal craniectomy is no longer used today. The main reason is that it is an invasive method with substantial postsurgical scars and complication rate. Since nowadays we have more deeply understood the pathophysiology of this disease and the important part of decreased CSF absorption, surgical diversion of CSF is a more scientifically correct choice.

Conclusion

Idiopathic intracranial hypertension is a disease with complex pathophysiological structure, which until now has not been fully clarified. The plurality of possible etiologies is the reason why many different treatments have been developed with a variety of response from patient to patient. The diagnostic methodology of IIH must include LP, MRI and brain venography. Treatment always begins with instructions to the patient for exercise, lifestyle modification and weight loss especially for obese people, combined in most cases with medication to reduce intracranial pressure. CSF diversion is the surgery of choice in patients with refractory headache with or without papilloedema and when vision is threatened optic nerve sheath fenestration must be performed. Bariatric surgery appears to be beneficial for obese people having difficulty losing weight with usual measures, while stent placement in venous sinuses should be the last resort when all previous treatment options for patients with radiologic and manometric confirmation of venous sinus stenosis have failed.

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