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Pseudotumor Cerebri (Idiopathic Intracranial Hypertension) an Update

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1. Introduction

1.1 History

Historically, several terms have been used to depict pseudotumor cerebri (PTC). In the late 1890's, Quincke (1893, 1897) was the first to describe and name this syndrome - "meningitis serosa" - patients suffering from headache, impaired visual acuity and papilledema. He related the symptoms to a state of elevated intracranial pressure and presumed it was caused by increased secretion of CSF by the autonomic nervous system. In 1904, Nonne (1904) termed this syndrome "pseudotumor cerebri" as the symptoms resembled a suspected intracranial mass. Foley (1955) renamed the condition "benign intracranial hypertension". However, in the late 1980's, Corbett et al (1982) altered the name to idiopathic intracranial hypertension, since the syndrome was not benign as once thought. In some cases, up to 25% of patients may lose their vision if appropriate treatment measures are not taken. At present, idiopathic intracranial hypertension is the accepted designation.

1.2 Demographics and epidemiology

Pseudotumor cerebri (PTC), also known as idiopathic intracranial hypertension (IIH) is a disorder of unknown etiology, predominantly affecting obese women of childbearing age (Ahlskog & O'Neill, 1982). In the general population, the annual incidence of PTC is estimated between 1-2 per 100,000 (Friedman & Jacobson, 2002, 2009). The incidence has been reported to have risen to 3.5 per 100,000 in women aged 20 - 44 years and may reach as high as 19 cases per 100,000 in women who are >20% over the ideal body weight (Durcan, 1988; Kesler et al 2001; Radhakrishnan et al., 1993, 1994).

PTC is uncommon in men, with female to male ratios reported approximately 4.3:1 to 8:1 (Binder et al, 2004; Durcan, 1988). The association between obesity and PTC is well established, >90% of women and >60% of men who suffer from this disorder are obese (Friedman et al., 2002; Radhakrishnan et al, 1994). The syndrome is relatively rare in the pediatric population. In the pre-pubertal population, it seems that obesity is not a risk factor. There is an equal distribution between boys and girls with an estimated incidence of approximately 1 case per 100,000.

1.3 Presenting signs and symptoms

Headaches, the most common presenting symptom in all age groups, occur in >90% of patients (Binder et al., 2004; Lessell, 1992). A PTC-associated headache has no specific

characteristics, but is usually more severe and different than previously described headaches. In PTC, the headache is most commonly bifrontal or generalized, usually occurring daily, but may also occur intermittently, worsening in the morning. When cerebral venous pressure is increased by the Valsalva maneuver, the headaches are often exacerbated and accompanied by neck pain.

Transient visual obscurations (TVO), the second most common symptom is more frequently reported in adult patients than in pediatric PTC patients, 72% vs. 2-53% respectively (Lessell, 1992). TVO may be unilateral or bilateral, usually lasting less than a minute and often precipitated by a change in posture. TVO indicate the presence of optic disc edema resulting in transient ischemia to the optic nerve head. Over half (60%) of PTC patients may experience pulsatile tinnitus as the initial complaint. Pulsatile tinnitus is thought to result from a turbulence created by higher to lower venous pressure around the jugular bulb (Binder et al., 2004).

In patients with PTC, focal neurological deficits are extremely uncommon. An alternative diagnosis should be considered when these deficits occur. Nevertheless, isolated 6th cranial nerve paresis, thought to be attributed to nerve traction from increased intracranial pressure has been observed in approximately 20% of adult cases (Binder et al., 2004). However, in children, the incidence was found to be as high as 50% (Cinciripini et al 1999; Lessell, 1992; Rangwala & Liu, 2007). Paresis of the 3rd, 4th, 7th or 12th nerve is extremely rare, occurring mostly in the pediatric population. Young children with PTC may present with irritability rather than headaches (Lessell, 1992), and may consequently develop signs of a posterior

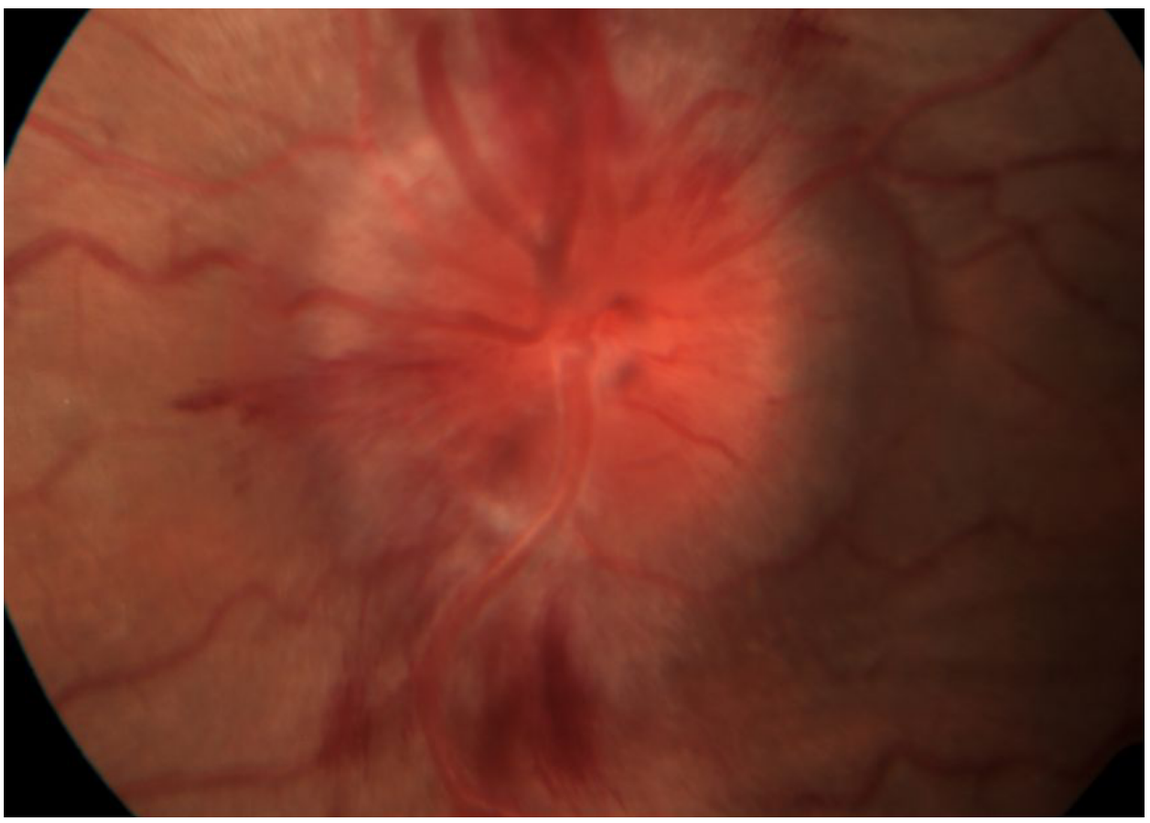

Fig. 1. Papilledema in a 26 year old PTC female patient.

fossa lesion, including ataxia, facial palsy, nuchal rigidity, malaise, torticollis (Lessell, 1992; Rangwala & Liu, 2007).

Papilledema is the diagnostic hallmark of PTC and is present in almost all patients (Mathew, 1996) (Figure 1). To note, although, unilateral cases may be encountered in approximately 10% of cases (Maxner et al., 1997; Wall & White, 1998) and a small number of patients may not have papilledema at all (Mathew, 1996; Wang et al., 1998; Winner & Bello, 1996), most cases occur either in very young infants with unfused sutures or in patients with anatomical variants of the endings of the optic nerve sheath (Hayreh, 1977; Killer et al., 1999).

Post-papilledema optic atrophy can occurs in untreated or inadequately treated patients after variable periods of time, usually over several months; in rare cases of fulminant PTC it can appear within weeks of the onset of symptoms. Some patients have persistent chronic papilledema without obvious visual deterioration. Visual field testing is the most sensitive method for detecting visual dysfunction. The most common abnormalities are an enlarged blind spot, generalized constriction and inferior nasal field loss.

1.4 Diagnosis

Diagnosis criteria for PTC were reviewed (Binder et al., 2004) (Table 1) and include signs and symptoms attributable to increased ICP, elevated CSF pressure with normal CSF content and normal neuroimaging studies. Other etiologies of intracranial hypertension were excluded. When these criteria are present, neuroimaging is employed to rule out space occupying lesions and sinus vein thrombosis. Lumbar puncture is subsequently performed to measure CSF opening pressure. Generally, an opening pressure of >250mm of water measured in a patient lying in the decubitus position, with outstretched legs and as relaxed as possible, is indicative of increased pressure. A pressure value between 201 and 249mm of water is inconclusive (Corbett & Mehta, 1983); pressure equal to or <200mm of water is considered normal. Often, due to CSF fluctuations, low or inconclusive measurements must be re-evaluated, especially if the clinical picture is indicative of increased ICP.

According to Tibussek et al (2010), a diagnosis of "probable PTC" would be indicated in patients, especially children, with clinical manifestations highly suggestive of PTC, but with a normal CSF opening pressure, presumably due to diurnal fluctuations. Rarely, in these circumstances, is a 24 hour intracranial CSF pressure monitoring, or transducer monitoring for 6 to 24 hours needed to confirm the diagnosis (Spence et al., 1980).

2. Neuroradiological evaluation

A detailed section in this chapter is devoted to diverse imaging modalities in patients with PTC. Imaging plays an important role in excluding intracranial tumors and structural or vascular lesions responsible for intracranial hypertension. CT, although adequate in ruling out hydrocephalus and most mass lesions, conditions such as sinus vein thrombosis, meningeal infiltration, and isodense tumors are undetected by a non-enhanced CT.

An MRI will detect almost all changes and by incorporating MRI venography will further enhance the ability to detect sinus vein thrombosis disguised as PTC (Crassard & Bousser, 2004). In rare cases, imaging of the spinal cord is essential as it excludes rare cases of spinal tumors that cause an increase in intracranial pressure. However, this is typically present with high protein levels in the CSF, therefore making it incompatible with the definition of PTC (Corbett & Mehta, 1983; Friedman & Jacobson, 2004; Ridsdale & Moseley, 1978). Traditionally, slit ventricles were thought to be present in PTC, but a quantitative analysis of

ventricular volume noted no differences between patients with PTC and age-matched control patients (Jacobson et al., 1990).
Signs of increased intracranial pressure that may be found on imaging studies include empty sella (70%), flattening of posterior sclera (80%), enhancement of the prelaminar optic nerve (50%), distention of the perioptic subarachnoid space (45%), vertical tortuosity of the orbital optic nerve (40%), and intraocular protrusion of the prelaminar optic nerve (30%) (Brodsky & Vaphiades, 1998).

1.	Symptoms, if present, represent increased intracranial pressure or papilledema.
2.	Signs represent increased intracranial pressure or papilledema.
3.	Documented elevated intracranial pressure during lumbar puncture measured in the lateral decubitus position
4.	Normal cerebrospinal fluid composition.
5.	No evidence of ventriculomegaly, mass, structural, or vascular lesion on magnetic resonance imaging or contrast-enhanced computed tomography and magnetic resonance venography or computerized venography for all others
6.	No other cause (including medication) of intracranial hypertension identified.

Table 1. Clinical criteria for diagnosing idiopathic intracranial hypertension (adapted from Binder et al 2004)

3. Pathogenesis

At present, the pathogenesis of the syndrome is still unknown, however, some explanation must account for elevated intracranial pressure with normal neuroimaging, CSF constituents and neurologic examination (Corbett, 2008). Intracranial pressure is maintained by cerebral arterial pressure which is cerebral autoregulated, resulting in constant intracranial pressure.
CSF is constantly absorbed into the superior sagittal sinus (SSS) at the pacchionian granulation level. This process is carried out by a pressure gradient between the CSF and the venous pressure in the SSS. When there is a rise in the venous pressure, the CSF pressure rises proportionately in order for the CSF to diffuse into the SSS.
According to the Montro-Kellie rule (Greitz et al., 1992; Mokori, 2001), the increase in ICP may be a result of various factors such as an increase in CSF, brain or blood volume. Although many studies have been performed, it is still unclear which factor is responsible for the increase in ICP in cases of PTC.
Different hypotheses have been proposed such as, an increase in cerebral blood volume which was originally proposed by Dandy in 1937. Raichle et al. (1978), using positron emission tomography (PET) found that almost no change occurred in the cerebral blood flow (CBF) in PTC patients, however there were markedly increased cerebral blood or water volumes.
A few years later, Brooks et al (1985) using PET, found no change in cerebral hemodynamics. Recently, Levine demonstrated that vascular compression and dilatation exist in the PTC patient (Levine, 2000).
Bateman et al. (2007) found that the total CBF measured by magnetic resonance (MR) flow quantification and MR venography in the PTC patient, was 46% more elevated then in the control group, which may be secondary to cerebral vascular autoregulation. On the other hand, Lorberboym et al. (2001) reported a reduction in perfusion, noted on single photon

emission CT scans in PTC patients a clear correlation between disease severity and CBF reduction. The proposed mechanisms for CBF changes are an increase of the cerebral vascular resistance, impairment of the CBF autoregulation, and a decrease of the tissue vascular density as a result of cerebral edema (Bateman, 2004)).

Bicakci et al (2006) recently studied 16 patients with perfusion and diffusion MRI, finding 6 patients with a statistically reduced CBF, and 2 with a marked increase. All other patients' cerebral blood volume did not significantly increase or decrease compared with the control group. Both vasodilatation and compression occurred in the PTC patient depending on the duration of the disease. The authors claimed that a long standing increase in CSF pressure might result in a decrease in CBF. On the other hand, an increase in CBF may be a result of a failure in autoregulation in the first phases of the disease, as suggested by Bateman's study.

4. Obstruction of venous outflow

The absence of ventricular dilatation in an elevated ICP condition is most likely explained by the presence of venous hypertension. As the pressure in the SSS rises, so does the CSF pressure due to hindered absorption of CSF. Brain parenchimal turgor increases due to an impending resorption of venous blood.

In 1995, King et al's (1995) series of 9 PTC patients with venous hypertension in the SSS and proximal transverse sinuses, cerebral venography and manometry were performed. The authors were able to observe the appearance of the transverse sinuses, ranging from a smooth tapered narrowing to a discrete intraluminal filling defect resembling mural thrombi.

The authors also found a significant drop in venous pressure at the level of the lateral third of the transverse sinus that was not fully explained by the anatomical finding on venography. Furthermore this gradient was eliminated after performing a cervical puncture which reduced the CSF pressure.

Karahalios et al (1996) also described a dural venous outflow obstruction found on cerebral venography and manometry in 5 out of 10 patients. A high pressure gradient was observed while those without obstruction had elevated right atrial pressure as well as elevated venous sinus pressure. The authors concluded that increased venous pressure was common in PTC, secondary to intracranial venous outlet obstruction and without anatomical obstruction.

In the same study, Karahalios proposed other hypotheses, such as obesity related cardiomyopathy with subsequent congestive heart failure, sleep apnea, carbon dioxide retention and increased intra-abdominal pressure. All these conditions benefited from diuretic therapy which reduced CSF production and also reduced the central plasma volume and hence venous pressure.

A recent study by Nodelmann (2009) observed that jugular vein valve insufficiency in patients with PTC supports the hypothesis that increased ICP may be a result of a more general state of venous hypertension, possibly associated with obesity.

Several studies focusing on the appearance of outflow obstruction on MRI and MRV (Farb et al, 2003; Johnston et al., 2002;) produced inconclusive results due to the wide variations of radiological appearances of posterior fossa dural sinuses, which may be confused with a normal anatomical variant (Lee & Brazis, 2000).

Higgins et al (2004) published a study comparing 20 patients with PTC who had undergone MRV and a control group of 40 healthy volunteers, strictly selected. Patients with a history of headaches or other signs or symptoms related to cranial venous involvement were

excluded. All subjects were matched for age and sex. A significant difference was observed in the appearance of the lateral sinus between the 2 groups; bilateral lateral sinus flow gaps were seen in 13 out of 20 (65%) PTC patients compared to none in the control group.

A new imaging method proposed by Farb et al. (2003) is auto-triggered elliptic-centric-ordered three-dimensional gadolinium-enhanced MR venography, which may be superior to time of flight MR venography in its flow insensitivity and decreased artifactual signal loss. Using this new technique, bilateral sinovenous stenosis was found in 27 out of 29 (93%) PTC patients compared to only 4 out of 59 (6.5%) in the control group. The authors concluded that the distal transverse sinus is the area of pressure gradient as described in King et al's study (1995).

Farb et al (2003) described two types of dural narrowing a "long smooth tapered narrowing", indicating an extra luminal compressive stenosis, and the "acutely marginated apparent intraluminal filling defect", indicating an enlarged, partially obstructing, intraluminal arachnoid granulation. They concluded that in PTC patients, increased dural venous pressure is measurable; however, whether this is a primary cause, a contributory factor, or a secondary phenomenon is uncertain.

Two opposing hypotheses can be made. The first proposes that dural sinus stenosis should be considered as the primary cause of PTC (fixed stenosis). Kollar et al. (2001) proposed that the transverse sinus is narrowed or obstructed by venous sinus thrombosis, vasculitis, congenital stenosis, enlarged arachnoid granulations or even heterotropic brain.

A recently published paper by De Lucia et al (2006) supports the suggested speculation that PTC is a long term sequela of previous sinus vein thrombosis or of an unidentified thrombus (Nedelmann et al., 2009; Sussman et al., 1997). In their study, 17 PTC patients without radiographic evidence of thrombosis were compared to healthy controls. The results showed a significant predominance of hypercoagulability markers, including protein C deficiency, increased plasma levels of prothrombin fragment 1 and 2, fibrinopeptide A, gene polymorphism for factor V leiden mutation, and high titers of cardiolipin antibodies.

The second hypothesis, in contrast to the fixed stenosis theory, suggests a dynamic one, where venous obstruction is the consequence and not the primary cause of intracranial hypertension. An increased intracranial pressure due to some unknown cause will result in a compression of the vascular compartment and dural sinuses which is in agreement with the Monroe-Kellie doctrine (Corbett, 2004). It is presumed that the predisposition to this phenomenon is due to the anatomy of the distal transverse sinus. Studies have shown that after normalization of the CSF pressure, resolution of the dural sinus narrowing occurs.

5. Endocrinological and metabolic factors

The association between PTC, female gender and obesity suggests an endocrine basis for this disorder. Reports of PTC occurring in corticosteroid deficient states such as Addison's disease, and following the removal of an ACTH secreting pituitary adenoma (Ross & Wilson, 1988), implies abnormalities in the adrenal pituitary axis. Furthermore, corticosteroids effectively treat PTC and corticosteroid withdrawal is associated with PTC (Yasargil et al., 1990). However, Soelberg Sørensen et al. (1986) found no consistent abnormality in pituitary, gonadal, thyroid or adrenal function. Multiple studies have documented the clear association between PTC and polycystic ovaries. In one study conducted by Glueck et al. (2003), 15 women out of 38 PTC patients were found to have

PCOS; 14 were obese, with a body-mass index (BMI) >30 kg/m² and 10 were extremely obese (BMI > or = 40).

6. Excess CSF production

Quincke (1893) was the first to describe excess CSF production. The rate of CSF production can be measured through invasive procedures (Walker, 2001). Donaldson found an increased CSF rate, while other studies failed to demonstrate CSF hypersecretion in PTC patients (Binder et al., 2004; Walker, 2001). A noninvasive technique (MRI) to measure CSF production by recording the flow through the cerebral aqueduct produced highly variable results, which did not support the theory of CSF overproduction in PTC patients (Gideon et al., 1994). In an attempt to rule out this theory, experimental infusion of artificial CSF was injected into the lateral ventricles of dogs which led to ventricular enlargement, not a PTC-like syndrome (Greitz et al., 1992; Walker, 2001).

7. CSF outflow reduction

This theory, supported by most studies, proposes the pathogenesis of CSF outflow obstruction into the venous system, although existing reports are still controversial. Studies have shown that PTC is associated with CSF outflow impairment (Calabrese et al., 1978; Cameron, 1933; Malm et al., 1992; Martins, 1974) and no histological evidence of arachnoid villi granulation dysfunction. Controversy exists as to whether impairment of CSF outflow at the arachnoid granulation level may be pathophysiological. In infancy, agenesis, deficiency, or dyslasia of the arachnoid villi and granulations result in hydrocephalus, not PTC (Gilles & Davidson, 1971).

Studies have demonstrated that in cases of elevated intracranial pressure attributed to high protein concentration in the CSF, (spinal tumor, Guillian-Barre syndrome), some patients develop hydrocephalus while others develop a PTC- like syndrome (Feldmann et al., 1986; Raichle et al., 1978; Ridsdale & Moseley, 1978; Ropper & Marmarou, 1984). It has been suggested that a high concentration of protein in CSF, may lead directly to impairment of CSF outflow.

8. Chronic inflammation

Recent reviews by Binder et al (2004) suggest that increased levels of cytokines and leptins (an adipocyte derivative hormone that circulates in the plasma at levels in proportion to body fat) in the CSF, may contribute to chronic inflammation and pathogenesis of intracranial hypertension in PTC patients.

Hypercoagulable states, devoid of obvious dural sinus thrombosis, have been reported associated with and in some cases used to explain PTC's mechanism. Kesler reported on several individuals found to have antiphospholipid antibodies and hyperfibrinogenemia related to thrombosis (Kesler et al. 2000; Kesler et al., 2010).

9. Drug associated

Numerous published reports and studies have described the correlation between certain drugs and vitamins and the development of increased intracranial pressure. These include antibiotics such as tetracycline or minocycline (Giles & Soble, 1971), fluoroquinolones

(Winrow & Supramaniam, 1990), naladixicacids (Cohen, 1973), sulfamethozaxole (Ch'ien, 1976) and hormonal treatments such as oral contraceptives, growth hormones, progesterone (Hamed et al., 1989; Rogers et al., 1999; Walsh et al., 1965), corticosteroid withdrawal (Neville & Wilson,1970), lithium (Saul et al, 1985) and vitamin A use and its derivatives (Morrice et al., 1960, Spector & Carlisle, 1984; Visani, 1996) in doses exceeding 50,000 UI in adults and over 20,000 UI in children.

10. Systemic conditions

In the literature, various systemic diseases have been found to be associated with PTC, the most common being uremia (Campos & Olitsky, 1995) Toxic conditions, hypervitaminosis A tetracycline therapy, lithium,prolonged steroid therpy, Steroid withdrawal,. Other diseases include anemia (Capriles, et al. 1963), dysthyroidism (Campos & Olitsky, 1995; Huseman & Torkelson, 1984), Addison's disease (Condulis et al., 1997) cerebral sinus thrombosis, and sleep apnea. .

11. Ancillary tests

11.1 Neuroimaging

The rationale for neuroimaging studies in PTC patients is twofold: prior to obtaining the cerebrospinal fluid, a brain imaging study is required to exclude any condition that would put the patient at risk of herniation, such as a tumor and to assure no secondary cause of increased ICP. The recommended study type has been modified together with the advance in neuroimaging technology. A CT scan is generally adequate as to ensure that the patient is not at risk when undergoing a lumbar puncture. The resolution is insufficient to exclude posterior fossa abnormalities, isodense lesions gliomatosis cerebri or venous sinus thrombosis. As either neuroimaging is acceptable, MRI of the brain with gadolinium is preferred over CT scanning with contrast.

11.2 MRI

Brain MRI is typically normal in the PTC patient, with a ventricular size normal for the patient's age. An asymptomatic empty sella is a well known neuroimaging finding in patients with increased intracranial pressure and may be present in over 50% of cases (Silbergleit et al., 1989). The empty sella (Figure 2) is attributed to longstanding effects of pulsatile CSF under high pressure, leading to downward herniation of an arachnocele through a defect in the diaphragma sella (George, 1989). The incidence of empty sella ranged from 10% when plain radiographs of the skull were analyzed (Sorenson et al., 1989) to 94% when third-generation CT scans were analyzed (Gibby et al., 1993).

Over the past few decades, other radiographic evidence of increased ICP in PTC patients has been detected using various neuroimaging techniques. Flattening of the posterior sclera is the most sensitive sign of elevated intracranial pressure, and was observed in 80% of patients with pseudotumor cerebri in Brodsky's study (Brodsky & Vaphiades, 1988). The flattening indicated transmission of elevated perioptic CSF pressure to the compressible posterior sclera. Jacobson (1995) found similar findings of bilateral posterior scleral flattening and distension of the perioptic subarachnoid space on MR imaging (Figure 3)in a patient with elevated intracranial pressure and unilateral papilledema. Furthermore, he emphasized that the constellation of acquired hyperopia and choroidal folds may indicate

the presence of pseudotumor cerebri in rare patients whose distal optic nerves are structurally resistant to developing papilledema.

A study by Jinkins et al (1996) found intraocular protrusion of the swollen optic disc in 10 out of 15 patients with pseudotumor cerebri while examining the prelaminar optic nerves via MRI. The optic disc appeared hypointense to vitreous on T2-weighted images.

Upon administration of intravenous gadolinium, enhancement on T1 and T2 was produced in areas where the blood-brain barrier was absent or disrupted. Intraocular enhancement of the swollen disc was found in 50% of MR images of patients with PTC resulting from diffuse prelaminar capillary leakage secondary to severe venous congestion. Distension of the perioptic subarachnoid space was present in 45% of patients with pseudotumor cerebri. A finding of intraocular protrusion of the prelaminar optic nerve can be visualized well on CT scanning (Lam et al., 1997; Jinkins et al., 1996), however, on MRI, no signal differential between the swollen optic disc and the vitreous cavity was observed (Connolly et al., 1992; Foley & Posner, 1975; 1989; Gass et al., 1996; Gideon et al., 1995; Mashima et al., 1996; Silbergleit et al.).

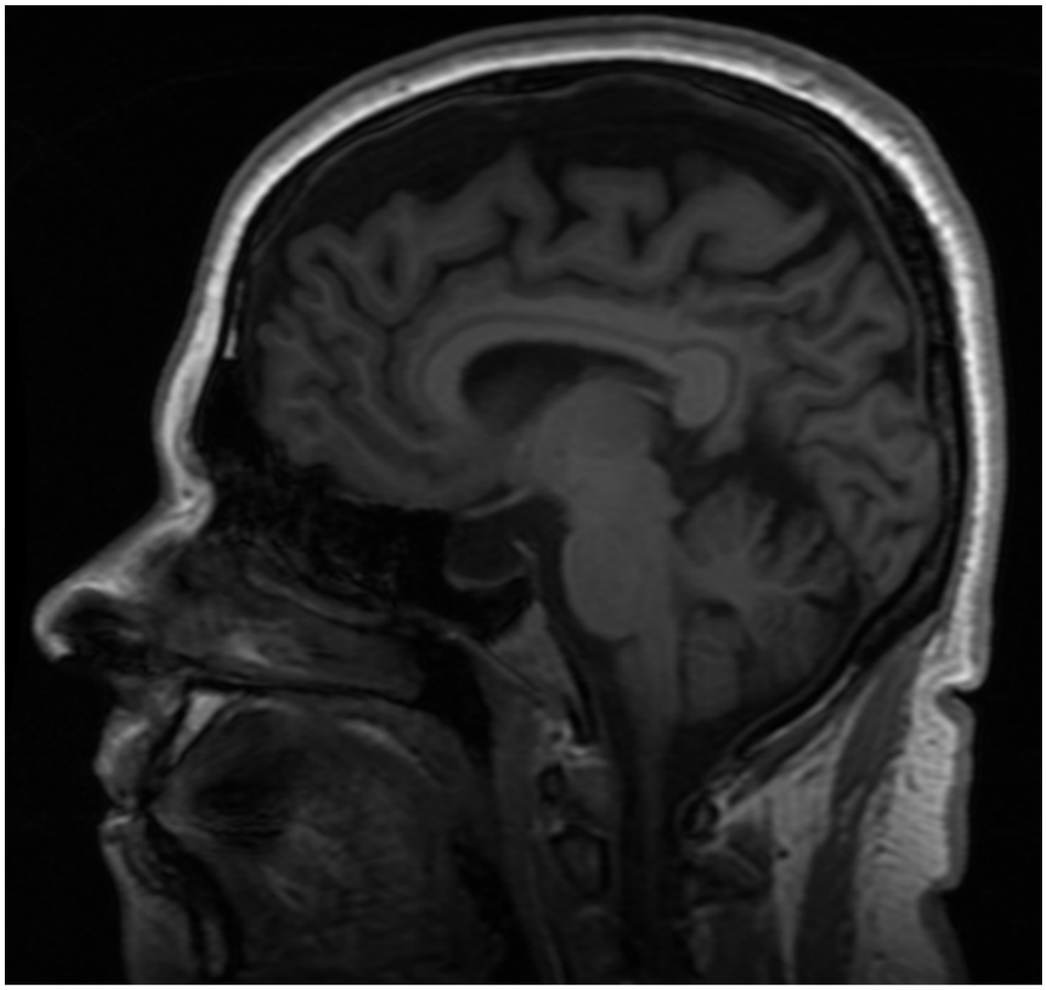

Fig. 2. MRI image demonstrating an empty sella in a 26 year old PTC patient

Brodsky (1998) observed vertical tortuosity of the optic nerves in 8 out of 20 (40%) patients with pseudotumor cerebri compared to only one control subject. Since some tortuosity may exist in normal subjects, the ability of axial MR imaging to display relatively minor degrees of horizontal tortuosity, makes it a relatively nonspecific finding. Furthermore, vertical tortuosity of the orbital optic nerve is often accompanied by a "smear sign" on T1-weighted images where the midportion of the optic nerve is displaced from the field of view, causing it to appear obscured by a "smear" of orbital fat. The optic nerve tortuosity or kinking in patients with elevated intracranial pressure is attributable to the distal fixation of the optic nerves by the globes tethered to the orbits by their rectus muscles and check ligaments.
Every patient suspected of PTC must routinely undergo an MRV or CTV examination. Both exams are equally reliable in identifying sinus vein thrombosis and therefore the decision of which examination to perform is entirely up to the expertise of the neurologist at the medical center.

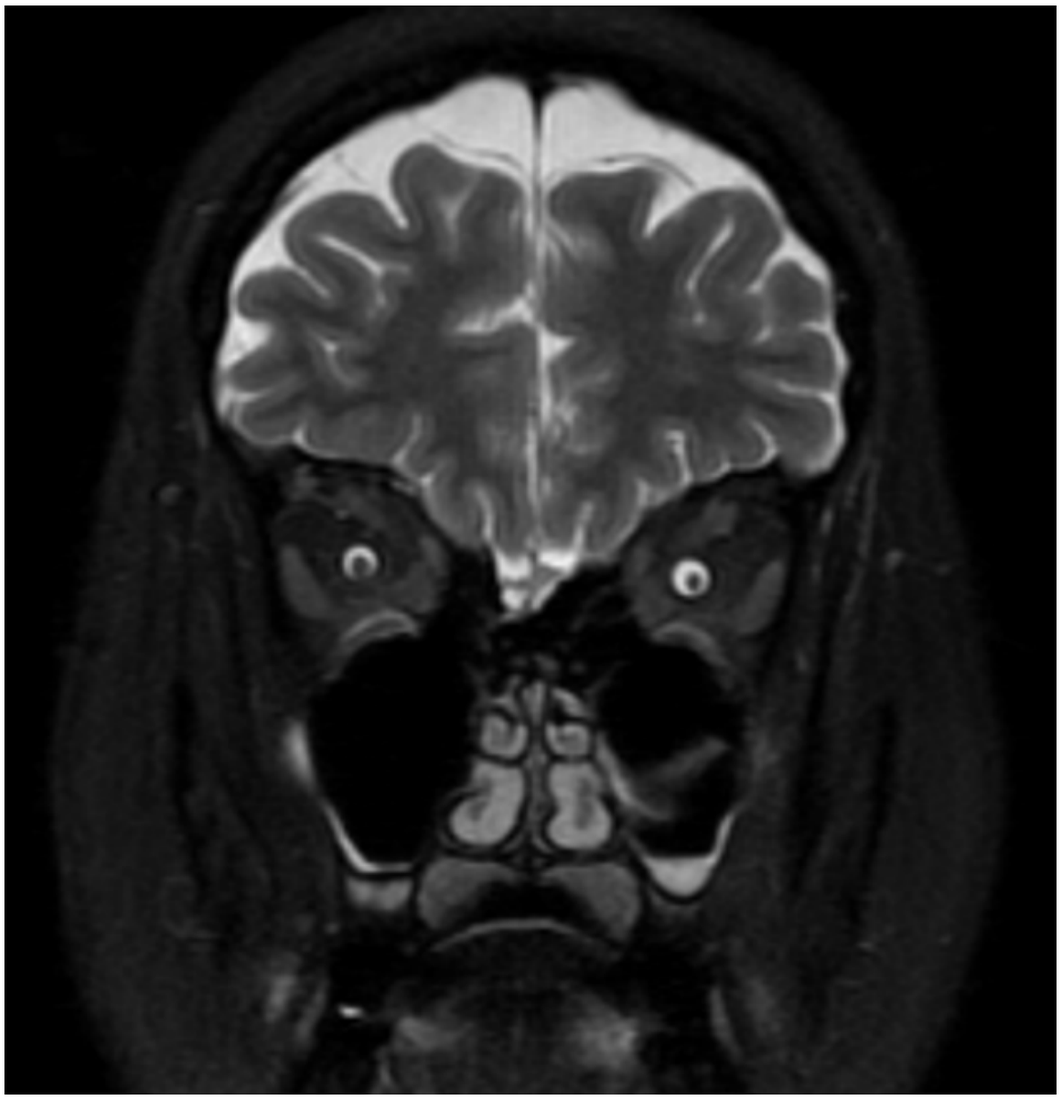

Fig. 3. Coronal T2 MRI image, demonstrating excess of CSF surrounding the optic nerves

11.3 MRV

PTC is consistently associated with venous outflow disturbances. Sinus venous stenosis are found on MR venography in the large majority of PTC patients and may have various conformations, ranging from functional smooth narrowing of sinus segments associated or not associated with definite flow gaps, to segmental hypoplasia or aplasia of one or more central venous collectors. Stenosis is currently believed to be a consequence of primary altered cerebrospinal fluid (CSF) pressure since it may normalize after CSF subtraction with lumbar puncture or shunting procedures (De Simone et al., 2010).

At present, the pathophysiologic mechanism of the elevated intracranial pressure in PTC remains unknown. Evidence suggests that perturbed venous efflux from the head may play a role in the etiology of the disease. Many studies suggest that elevated intracranial venous pressure, an underlying component of PTC, is the result of intracranial venous hypertension due to raised central venous pressure or disturbances of transverse sinuses (TSs) outflow (Brodsky et al., 1998; Friedman & Jacobson, 2002; Gass et al., 1996; Jacobson et al., 1990).

Occasionally, the clinical picture of PTC is the only clue to the presence of cerebral venous thrombosis, which may be a potentially devastating condition. Thus, every patient diagnosed with PTC must undergo an MRV or CTV to rule out this condition.

MRV is a noninvasive technique effective in visualizing cerebral venous sinuses (Mattle et al., 1991). Different MRV sequences offer the capability of investigating cerebral sinovenous outflow from multiple orientations such as two-dimensional time-offlight (2D-TOF) and three-dimensional phase-contrast (3D-PC) techniques. However, all these techniques have limitations and pitfalls (Ayanzen et al., 2000; Pipe, 2001).

A prospective study by Farb et al. (2003) suggested an auto-triggered elliptic-centric-ordered three-dimensional gadolinium enhanced MR venography (ATECO MRV) to evaluate the cerebral venous outflow of patients with PTC in combination with a novel scoring system. They found substantial bilateral sinovenous stenoses in 27 out of 29 (93%) patients with PTC compared to only 4 out of 59 in the controls and concluded that using ATECO MRV and a novel grading system for quantifying sinovenous stenoses, the authors could identify PTC patients with a sensitivity and specificity of 93%.

Higgins et al. (Higgins et al., 2004) described a distinctive pattern in the signal phase of contrast MRV in PTC patients. They found "signal gaps" in both lateral sinuses of PTC patients, unobserved in their control group. These "signal gaps" may indicate that flow velocities over that specific segment are outside the range prescribed in their study.

This finding does not necessarily mean that a thrombus is present nor does it inevitably indicate that abnormal arachnoid granulations might have caused a local alteration of blood flow. However, it does raise the possibility of stenosis or occlusion.

Higgins et al. (2002) reported the first patient with refractory PTC and transverse sinus stenosis treated with a stent. Direct cerebral venography and manometry confirmed the presence of stenoses with raised pressure, proximal to the obstructions. Dilation of one of the sinuses with a stent reduced the pressure gradient with dramatic symptomatic improvement.

Current evidence (Higgins et al., 2003; Metellus et al.; Ogungbo et al., 2003; 2005; Rajpal et al., 2005) suggests that selected patients with PTC may benefit from a transverse sinus (TS) stent. Restoring the patency of stenotic TSs with a stent in patients with refractory IIH resulted in a resolution or significant improvement in headache and papilledema.

11.4 CT and CTV

Neuroimaging utilizing CT offers rapid image acquisition, wide availability and excellent spatial resolution. The speed and ability of a CT to detect acute blood or bone abnormality makes this technique very valuable in traumatic cases.

Due to the rise in availability of MRI and MRV during the past few decades, and their known advantages over CT scans, the use of a CT as a neuroimaging tool in diagnosing PTC patients has lessened over the years. Current studies in the literature are focusing mainly on MRI and MRV findings in neuroimaging rather the CT.

Almost 25 years ago, Jinkins (1987) first reported on the reversal of the optic nerve head in a variety of conditions associated with increased intracranial pressure, including pseudotumor cerebri. Enlarged optic nerve sheaths have also been observed in patients with pseudotumor cerebri. Weisberg (1985) found that 2/28 patients had enlarged optic nerves, although no measurements were provided and no control values were available. Six out of 28 patients were described as having a "small-sized ventricular system." These examinations were performed on a second-generation CT scanner, without controls and in a non-blinded manner.

Almost two decades ago, Gibby et al. (1993) published a paper on CT findings in their PTC patients. The purpose of their study was to evaluate and compare orbital and cerebral CT findings in PTC patients with those of age and sex matched controls. Ventricular size in both groups was evaluated. Their findings matched Huckman et al's (1976) who found no differences between ventricular sizes of patients with pseudotumor cerebri and those of a control population.

Empty sellae have been associated with many conditions causing increased intracranial pressure. Gibby et al. in 1993 observed empty sellae in 5% of 788 autopsies (Kesler et al., 2001). In the PTC group, 16 (94%) out of 17 patients had at least partial empty sella. The degree of empty sellae was significantly greater than in the controls. The high prevalence noted in patients with pseudotumor cerebri is compatible with their chronic elevated intracranial pressure, which averaged 370 mm H2O. CT angiography uses a high speed spiral scanner, providing excellent vessel resolution with a 3-dimensional capability, comparable to an MRA. The technique requires iodinated dye and ionizing radiation and takes approximately 15 minutes. Sensitivities in detecting aneurysms >3mm or stenosis >70% are approximately 95%. Some centers prefer the use of a CTA over an MRA in identifying cerebral aneurysms, including those causing ocular motor cranial nerve palsies.

11.5 Visual field perimetry

Visual field testing by either automated Humphrey static or manual Goldmann perimetry reveals enlargement of the physiological blind spot in virtually all patients with PTC. Other common visual field defects include inferonasal loss and generalized constriction of the fields. Central defects, arcuate and altitudinal defects may occur but are highly unlikely. However, if found, a search is warranted for another cause, unless a large serous retinal detachment from a high-grade optic edema, spreading to the macula area, is found.

Almost all PTC patients suffer from some type of visual field loss over time. In prospective (Wall & George, 1987; Wall & George, 1991) studies of patients with PTC, visual field loss in at least 1 eye (other than an enlargement of the blind spot due to the edematous optic nerve) was found in 96% of patients using a Goldmann perimetry, a disease specific strategy and in 92% with automated perimetry. Approximately one third of this visual field loss was mild and was usually not noticed by the patient (Wall & George, 1991).

Wall et al's study (1991) showed that with treatment, about 50% of patients experience a significant visual field improvement. They further demonstrated that the only subgroup of patients who had a worsening of their visual fields were those with a recent weight gain. This was the only factor significantly associated with a decline in vision.

11.6 Ultrasound of optic nerve

Ultrasound has been used to identify intracranial hypertension by measuring the optic nerve sheath diameter. The modality is extremely safe and does not have any contraindications for use, except for ocular globe injuries (Munk et al., 1991). In most modern medical facilities, multipurpose ultrasound units with high-frequency transducers (>7.5 MHz) provide high lateral and axial precision (Berges et al., 2006).

Hayreh (1964) in an experimental study of monkeys and humans showed that the subarachnoid spaces surrounding the optic nerve is in continuity with the intracranial cavity, and therefore changes in cerebrospinal fluid pressure may be transmitted along the optic nerve sheath (Hayreh, 1964). The retrobulbar enlarged optic nerve sheath can therefore inflate as a consequence of raised pressure in the cerebrospinal fluid.

It has been confirmed that the optic nerve sheath diameter (ONSD) increases in patients with intracranial hypertension (Blaivas et al., 2005; Geeraerts et al., 2007; Girisgin et al., 2007; Karakitsos et al., 2006; Malayeri et al., 2005; Munk et al., 1991; Salgarello et al., 1996; Stone, 2009). ONSD alterations are correlated with head CT scan results in brain injured adults (Karakitsos et al., 2006) as well as with the invasive and noninvasive measurements of the ICP (Soldatos et al., 2008).

During US evaluation, it is important to perform a 30° test to evaluate excess of fluids within the arachnoid sheaths of the optic nerve. The patient is asked to turn approximately 30° toward the probe placed temporally on the globe. The measurements in abduction are compared with the measurements at the primary position. If fluid excess is present, the diameter at 30° will be smaller than that found in the primary position.

11.7 Optical coherence tomography (OCT)

OCT is a non-invasive imaging technique yielding high-resolution, cross-sectional images of the retina. More importantly, it is a valuable modality used to identify the status of the retinal nerve fiber layer as well as to measure macular thickness. The technique is principally based on measuring the time required for light to reflect from the tissue to an external detector (i.e. "echo time delay"). Duration of time and intensity of the backscattered light corresponds directly to the depth and density of the tissue being imaged. OCT produces in vivo cross-sections which can be serially acquired (in thin sections) in order to obtain tomographic images (Schuman et al., 2004).

The principles underlying OCT are similar to those of ultrasound imaging, except that light is utilized instead of sound. The axial resolution of OCT images is at least 1-2 orders of magnitude greater than those of ultrasound. OCT images of the retina provide a spatial resolution as low as 3-5 microns (Huang et al., 1991; Schuman et al., 2004).

Currently, two main types of OCT are utilized in practice: the time-domain, employing low-coherence interferometry for imaging tissue structures, and the spectral-domain OCT. Spectral-domain imaging provides faster and more spatially detailed images than the time-domain method. In addition, spectral domain OCT allows for imaging at a speed of 18,000 to approximately 40,000 A-scans per second, fast enough to eliminate artifacts from

eye movements. It also provides a greater resolution of the retina with subsequent better visualization of the laminar structure and clarification of details at the cellular level within the nuclear layers (Choi et al., 2008). Several reports have also described particularly good reproducibility of RNFL and optic disc measurements with the newer spectral-domain technique (Gonzalez-Garcia, et al., 2009; Leung et al., 2009; Menke et al., 2008).

Computer-aided image processing algorithms have been developed to estimate NFL thickness from circumpapillary OCT images acquired in cylindrical sections surrounding the optic disc. A circumpapillary scan pattern of a typically ¾ mm diameter is used, because it effectively intercepts all nerve fibers originating from the optic disc, thus enabling a quantitative measurement of the circumferential variations in NFL thickness around the optic disc as well as visualization of the nerve fiber bundles.

Studies have demonstrated the effectiveness of time-domain OCT in providing a quantitative measure of the severity of disease, response to treatment and follow up monitoring of patients with PTC (Ophir et al., 2005; Rebolleda & Munoz-Negrete, 2009). RNFL thickness decreased correspondingly, with the improvement recorded at the patients' clinical evaluation. The study outcomes provided a basis for using OCT to predict which patients would ultimately fare better in terms of visual functional status (Rebolleda & Munoz-Negrete, 2009).

Precise measurements obtained with OCT allow the physician to more accurately evaluate the treatment effect than the subjective interpretation of the funduscopic appearance of the optic nerve heads. Recently, studies have emphasized the importance of viewing the macula in these patients. Hoye et al. (2001) evaluated the detection and monitoring of sub-retinal fluids extending from the optic nerve head to the macula in patients with papilledema. The authors found that the fluids accounted for the reduced visual acuity in 7 out of 55 patients, and when the volume of sub-retinal fluids decreased, an improvement in the visual acuity function was noted.

Future OCT assessment of papilledema will be evaluating the total optic nerve head disc volume and maximal optic nerve head height, as these measures potentially correlate with the response to medication and ultimate visual outcome. At present, clinical evaluation of the optic nerve head volume, better reflects the overall degree of optic nerve head edema rather than the thickness of the RNFL alone, since volume measurement incorporates the volume of both the total optic nerve height and the sub-retinal hypo reflective space. (Johnson et al., 2009).

11.8 Fluorescein angiography

Fluorescein angiography was initially developed as a tool for studying retinal vascular flow characteristics. Extensive use of fluorescein angiography and technique refinement has allowed the clinician and researcher to better understand the pathophysiologic and histopathologic changes of fundus disease in vivo. Fluorescein angiography may aid the clinician in accurately diagnosing papilledema by the appreciation of leakage or late hyperfluorescence surrounding the optic disc. Blocked hypofluorescence may be noted at the optic nerve head during papilledema as a result of bleeding, which is present at the level of the neurosensory retina, blocking the fluorescence from the underlying choroid (Rabb et al., 1978).

12. Management

There are nonsurgical and surgical approaches to PTC, decisions based on symptomatology and visual function status. If a headache is controlled by common analgesics and no optic nerve dysfunction is observed, therapy may not be required. Asymptomatic patients with preserved vision and minimal papilledema warrant only frequent follow-ups as well as monitoring disc swelling and visual function, including visual fields (Nonne, 1904).

12.1 Medical (nonsurgical) approach

Acetazolamide, a carbonic anhydrase inhibitor that decreases CSF production by the choroid plexus, is generally accepted as first-line medication, although its efficacy has not been proven in prospective trials. Based on our experience, a starting regimen of acetazolamide 500 mg, orally two or three times per day, is preferred. The dose can be increased to a total of 3 grams per day, if necessary. Major side effects include diuresis, loss of appetite, abnormal taste (metallic taste with carbonated beverages) paresthesias of the lips, fingers and toes, malaise, renal colic and metabolic acidosis (Corbett et al., 1982). Most of these side effects resolve with potassium and magnesium-rich dietary supplements such as bananas and oranges. Severe adverse effects experienced with acetazolamide treatment include acute tubular necrosis, hepatic dysfunction, and aplastic anemia.

Teratogenic effects in animals such as limb malformations and cortical dysgenesis have been reported (Quincke, 1893). Although sacrococcygeal teratoma in neonates (Tibussek et al., 2010) have been documented in the past, there is little clinical or experimental evidence to support any adverse effect of the drug on pregnancy outcome in humans (Spence et al., 1980). If acetazolamide fails, topiramate, an anti-epileptic drug, may be used. Its therapeutic effects are due to its carbonic anhydrase inhibitory properties. The drug is particularly useful as a prophylaxis for headaches, appetite suppression and weight loss (Nonne, 1904). The dose should be built up slowly over weeks (25 mg/week) in order to reduce the risk of cognitive side effects. It is of utmost importance to regularly check the intraocular pressure (IOP) of patients undergoing this treatment, as elevation of IOP is a known side effect of topamax.

Short-term oral corticosteroids may be considered as a treatment option in patients presenting with severe headaches, marked papilledema, and very high intracranial pressure. High doses of intravenous corticosteroid treatment may occasionally be administered when there is rapidly progressive vision loss or while the patient awaits surgery (Mathews et al., 2003).

Treatment medication is usually given over a long period of time. ICP-lowering agents may be tapered and eventually discontinued when the patient's visual status and optic nerve appearance have improved and stabilized. Patients should be periodically monitored post treatment, since recurrences are common. If symptoms reoccur, reinstitution of medications is usually indicated (Friedman & Jacobson, 2004).

Weight loss is a crucial part of the treatment program, as even moderately obese patients may significantly benefit from a sensible diet and exercise program (Mathews et al., 2003). Medications known as associated risk factors for pseudotumor syndromes, such as vitamin A, vitamin A derivatives, and tetracycline should be discontinued if possible.

12.2 Lumbar puncture

In the past, repeated lumbar punctures were an acceptable treatment modality due to improvement of symptoms after the procedure. Nowadays, this type of treatment approach

is less acceptable. Currently, lumbar puncture may be indicated in pregnant women or when the clinical picture points to rapidly declining vision, thus temporarily lowering the CSF pressure while planning a more aggressive treatment (Friedman & Jacobson, 2004). In the past serial lumbar punctures (e.g., twice weekly) have been proposed as an alternative to surgery for patients with papilledema, when the disease cannot be controlled medically. Complications of the procedure such as infection, tonsillar herniation, radiculopathy, and arachnoiditis are rare.

12.3 Surgical approach

The most frequent and accepted indication for surgery is a progressive loss of vision despite maximal medical therapy. Surgery should be carried out as soon as a visual field defect worsens or remains unimproved despite maximal treatment. Medical treatment fails in approximately 18% to 22% of patients with PTC (Burgett et al., 1997; Corbett & Thompson, 1989; Lorberboym et al., 2001; Lueck & McIlwaine, 2002; Pearson et al., 1991). According to Friedman et al (2004), ophthalmological indications for surgical intervention are severe or rapid visual loss at onset ("malignant IIH"), severe papilledema causing macular edema or exudates without improvement while undergoing medical treatment. Even if there is no consensus among the specialists (Friedman & Jacobson, 2004), surgery should be considered in the management of intractable headaches (Binder et al., 2004; Mathews et al., 2003). Surgical treatment options include optic nerve sheath fenestration (ONSF) and CSF diversion procedures. A CSF shunt reduces intracranial hypertension, whereas ONSF focuses on protecting the vulnerable optic nerve head.

12.4 Optic nerve sheath decompression (ONSD)

The mechanism by which ONSD works has not been clarified, but several theories have been suggested. Keltner (1988) suggests that it may provide a filtering effect, with a subsequent decrease in the local CSF pressure, improvement of the peripapillary circulation (Keltner, 1988), or produce a generalized decrease in ICP. According to another hypothesis, the scarring of the arachnoid by the procedure itself may protect the nerve head from elevated CSF pressure (Friedman & Jacobson, 2004). Technically, ONSD is performed by uncovering the optic nerve sheath through a lateral orbitotomy or through a medial approach via a transconjunctival incision. Multiple linear incisions are made or a window is cut into the anterior dural that covers the optic nerve sheath, creating a CSF drainage outlet (Mathews et al., 2003).

The overall complication rate of ONSD ranges from 4.8% to 45% (151,165,166,167,168), the most common being extraocular motility problems due to lateral rectus palsy which is usually transient, and papillary abnormalities. Other complications may include long-term and transient blindness due to ischemic injury to the optic nerve, orbital hemorrhage, visual field defects and globe perforation (Friedman & Jacobson, 2004). In the majority of patients, post-ONSD vision stabilizes or improves in the long-term, but as many as 32% of operated eyes may experience deterioration following initially successful surgery (McHenry & Spoor, 1993). A reoperation can be performed, but based on clinical experience, a shunting procedure is recommended in these cases.

12.5 Lumbar peritoneal shunt (L-P shunt)

Although an L-P shunt is considered an effective procedure, failure and low pressure-related headaches are common. Shunts may be efficiently placed in the lumbar cistern,

cisterna magna, or the ventricles. The lumboperitoneal (L-P) technique has traditionally been the method of choice in PTC.

A review of the literature Binder et al (2004) found that the efficacy of L-P shunting is maintained as long as the shunt remains patent. The failure rate for LP shunts range from 38% to 64% (Burgett et al., 1997; Gupta et al., 2007; Johnston et al., 1988). Major causes include catheter obstruction, over-shunting (low pressure headaches), catheter migration, and lumbar radiculopathy.

12.6 Ventriculoperitoneal (V-P) shunts

A V-P shunt is difficult to perform due to relatively small or normal ventricle size. However, this technique is becoming increasingly popular in treating PTC (Binder et al., 2004; Maher et al., 2001; Tulipan et al., 1998).

In the long-term, V-P shunts offer advantages compared to the L-P shunt method, especially with regard to shunt revision (Kang, 2000; Maher et al., 2001). The procedure does not present the risk of inducing a Chiari I malformation, and may be less likely to over-drain.

A wider range of shunts are available for the V-P route. Usually, PTC patients benefit from relatively high-pressure valves (possibly with an antisiphon system to limit over-drainage), which are able to retain sufficient intracranial CSF to compensate the changing intracranial volume conditions and limit the collapse of the ventricular system around the shunt catheter. Flow-regulated valves have also been proposed (Garton, 2004).

12.7 Subtemporal decompression

The first neurosurgical technique to treat PTC patients, by a subtemporal decompression, was performed in 1937 (Dandy, 1937). Dandy performed a unilateral subtemporal craniectomy with excellent initial results in alleviating headaches and preventing visual loss. The long-term efficacy of the procedure was uncertain, since a high rate of morbidity and complications were reported, including seizures, infections, focal brain damage, cosmetic disfigurement, intracranial hematomas, and further visual deterioration (Binder et al., 2004). After introducing stenting procedures for treating IIH, this procedure became obsolete; nonetheless, subtemporal decompression is still an option, when other surgical methods have failed.

12.8 Endovascular stenting

It is highly controversial whether venous sinus narrowing is the cause or the result of elevated intracranial pressure. Based on the frequent findings in MRI venography of narrowed transverse sinuses, endovascular stenting of the venous sinuses has been recently advocated by some authors (Higgins et al., 2002; Higgins et al., 2003; Metellus et al., 2005; Metellus et al., 2007; Donnet et al., 2008; Paquet et al., 2008).

Higgins et al (2002) was the first to report on a 30 year old patient with refractory PTC, papilledema and bilateral TS stenosis found on an MR venogram, that was successfully treated with dilation of 1 of the sinuses with a stent, thus reducing the pressure gradient with dramatic symptomatic improvement.

As of today, only about 40 patients with PTC, treated with sinovenous stent placement, have been reported in the literature. Most were women aged 15-65, symptomatic with PTC for 2 weeks to 15 years. After stent placement, 33 out of the 40 (82.5%), reported a significant improvement in their headaches. Papilledema improved or resolved in 30 out of 33 (91%)

patients who presented with active papilledema. Although the promising initial results of long term efficiency of the procedure still needs to be proven, further investigation is still warranted to prove the procedure as a useful treatment technique.

12.9 Pregnancy and PTC

Current reports suggest that pregnant patients with PTC can be safely managed similarly to nonpregnant patients with PTC. No increase in the rate of spontaneous abortion or fetal wastage has been reported. A therapeutic abortion to limit the progression of the disease is not indicated. (Tang et al., 2004).

Acetazolamide had previously been considered as the preferred therapy after 20 weeks of gestation, since sacrococcygeal teratoma was reported with earlier use (Digre et al., 1984). A recent report of 12 women treated with acetazolamide for PTC during pregnancy, showed no adverse pregnancy outcomes in terms of fetal loss or congenital malformation. Acetazolamide at high doses may produce birth defects in animals, but there is little clinical or experimental evidence to support any adverse effect on pregnancy outcome in humans. If the clinical situation mandates acetazolamide use in PTC, the drug can be offered after appropriate informed consent (Lee et al., 20050). Management of labor and indications for cesarean delivery for a parturient with PTC are controversial. Regular labor may be allowed with a cesarean delivery reserved for obstetric indications.

13. Natural history and visual prognosis

The natural history of PTC is unknown. In some cases, it is a self-limited condition, while in others ICP may remain elevated for many years even if systemic and visual symptoms resolve. In some patients, the process may last from months to years. Individuals with mild to moderate visual loss tend to recover vision following medical therapy. Papilledema usually resolves after a few weeks or months, but many patients are left with some residual disc elevation, especially nasally. Severe visual impairment may be a serious and permanent complication of PTC. PTC produces significant visual impairment in approximately 25% of patients. The risk of visual loss in the pediatric PTC population is similar to that of adults (Corbett & Thompson, 1989). Recurrent symptoms have been reported in 8 to 37% of patients, years after being diagnosed (Corbett & Thompson, 1989). Visual deterioration in PTC patients is usually gradual, but in cases of fulminant papilledema, blindness may appear rather quickly. In Corbett et al's (1989) follow up study of 5 - 41 years after the initial diagnosis of 57 patients, revealed severe visual impairment in 14 patients (24.6%). In Kesler et al's experience (2004), recurrence was frequently associated with weight gain. The long-term prognosis and visual outcome of 54 patients with IIH was observed over a period of 6.2 years. The results showed that recurrences occurred in almost 40% of the cases. None of these exacerbations occurred during the first 10 months, and none occurred while the patients continued treatment.

14. References

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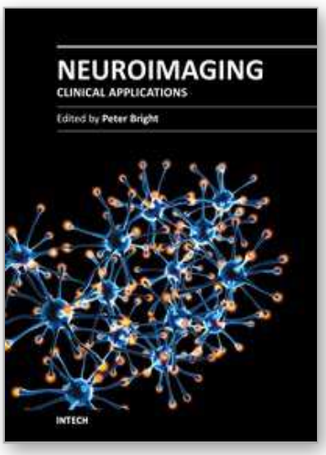

Neuroimaging - Clinical Applications
Edited by Prof. Peter Bright

ISBN 978-953-51-0200-7
Hard cover, 576 pages
Publisher InTech
Published online 09, March, 2012
Published in print edition March, 2012

Modern neuroimaging tools allow unprecedented opportunities for understanding brain neuroanatomy and function in health and disease. Each available technique carries with it a particular balance of strengths and limitations, such that converging evidence based on multiple methods provides the most powerful approach for advancing our knowledge in the fields of clinical and cognitive neuroscience. The scope of this book is not to provide a comprehensive overview of methods and their clinical applications but to provide a "snapshot" of current approaches using well established and newly emerging techniques.

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Eldar Rosenfeld and Anat Kesler (2012). Pseudotumor Cerebri (Idiopathic Intracranial Hypertension) an Update, Neuroimaging - Clinical Applications, Prof. Peter Bright (Ed.), ISBN: 978-953-51-0200-7, InTech, Available from: http://www.intechopen.com/books/neuroimaging-clinical-applications/pseudotumor-cerebri-idiopathic-intracranial-hypertension-an-update

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