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Review Article

Papilloedema: Etiology and its Management

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Abstract

A swelling of the optic nerve head caused by an increase in intracranial pressure is known as papilledema (ICP). Unlike other forms of disc edema, it frequently presents with normal visual function throughout the acute period. We should rule out pseudo papilledema and suspect an intracranial tumor while assessing the patient. Axoplasmic transport inside ganglion cell axons is impeded by high intracranial pressure (ICP) that is transmitted to the subarachnoid area surrounding the optic nerve, resulting in papilledema. There is an ongoing debate about whether microvascular ischemia or physical constriction of axons causes axoplasmic flow standstill. The most common cause of papilledema is idiopathic intracranial hypertension (IIH), which can also result from space-occupying intracranial lesions, meningitis, subarachnoid hemorrhage or trauma, cerebral venous thrombosis, cerebral edema from blunt trauma to the head, severe systemic hypertension, and very rarely, hypersecretion of CSF by a choroid plexus tumor. Clinical features include headache (early morning), nausea (projectile), deterioration of consciousness, transient visual obscuration (vision is generally normal), and horizontal diplopia. Magnetic resonance imaging (MRI) of the brain and orbits, neck, and spine, with venography sequences is the preferred neuroimaging modality performed to look for indirect imaging signs of increased ICP and to rule out non-idiopathic causes. Lumbar puncture with measurement of opening pressure and evaluation of CSF composition. Computed tomography of the chest, complete blood count, and creatinine testing should be able to identify most secondary causes of intracranial hypertension. The underlying cause of papilledema patients' symptoms should be the focus of their treatment.

Keywords: *Papilledema; Idiopathic Intracranial Hypertension; Pseudopapilledema*

Introduction

Papilledema is the name for disc swelling that results from elevated intracranial pressure (ICP). It can't exist without high ICP, yet high ICP can happen without papilledema. If intracranial pressure is kept elevated, orthograde axoplasmic flow stasis occurs at the optic nerve head, which causes edema and axon loss. It can be unilateral or asymmetric, but it is usually bilateral and symmetric. Idiopathic intracranial hypertension (IIH) is the most common cause, particularly in people under 50. The majority of IIH patients benefit from oral acetazolamide and weight loss. When a patient presents with reduced central acuity and narrowed visual fields, or when they do not improve with acetazolamide treatment, ventriculoperitoneal shunting surgery should be investigated as a surgical option [1]. It reduces cerebrospinal fluid (CSF) outflow by either generating CSF derangements or manually obstructing CSF outflow channels. Seldom do situations arise that increase CSF output [2].

Epidemiology

It can develop in any age range, in either sex, in any race or ethnicity, and it can take on different forms depending on the specific study and context in which it is recorded. The majority of obese women of reproductive age are seen to have idiopathic intracranial hypertension; among these women, the incidence is 13 per 100000 in the age group of 20 to 44, while the annual incidence in the general population of the United States is estimated to be 0.9 per 100000 [3].

Pathogenesis of papilledema

The optic nerve, which is connected with the brain's subarachnoid space and is covered in all three meningeal layers, is made up of glial cells and axons from retinal ganglion cells. Because the CSF surrounding the optic nerve and the intracranial CSF is continuous, increased ICP can be conveyed straight to the optic nerve. The theory is that this causes retrograde axoplasmic flow across the optic disc, which leads to disc edema and optic neuropathy, by upsetting the normal pressure gradient across the intraocular and orbital optic nerve. Regarding the cause of this, there are conflicting theories: either ischemic damage to the axons or mechanical compression [4]. The Monro-Kellie doctrine describes the pressure-volume relationship between intracranial pressure (ICP), cerebral perfusion pressure, blood volume, brain tissue, and CSF volume. Since the combined volume of the blood, CSF, and brain inside the cranium is fixed, any increase in one of these components must be balanced out by a decrease in the volume of the other components, otherwise, elevated intracranial pressure (ICP) may occur [5].

Mechanism and pattern of visual loss

Axoplasmic flow standstill is probably the primary cause of vision loss. Elevated intraocular pressure (ICP) results in increased extraocular pressure (CSF) surrounding the optic nerves. This disrupts the typical intraocular pressure-to-retrolaminar pressure gradient, raising the tissue pressure inside the nerves. The metabolic mechanisms that mediate axoplasmic flow are disrupted by the elevated tissue pressure inside the neurons [6-8]. The most frequent alteration to the visual field occurs when papilledema enlarges the blind spot during the acute stage [9]. Prolonged and severe papilledema can lead to abnormalities in the nerve fiber layer of the visual field. The injury to the nerve fiber bundles at the level of the optic disc is linked to the common visual field abnormalities observed in papilledema [10]. Up until the disease's final stages, the papillomacular bundle and consequently central visual acuity appear to be spared [11].

History

Papilledema can also be asymptomatic. Transient visual obscuration caused by brief ischemia to the optic nerve head. However, if left untreated or if symptoms appear later, long-standing or fulminant papilledema may cause severe loss of peripheral visual field and eventually spread to include central vision. Unilateral or bilateral sixth nerve palsies are non-localizing neurological signs that can cause intermittent or continuous binocular diplopia. Headaches, nausea, vomiting, and pulsatile tinnitus are examples of systemic symptoms. The characteristics of a headache are usually positional, with mornings and lying down being the worst times. High intracranial pressure causes turbulence in the venous system, which results in pulsatile tinnitus. Previous space-occupying lesions, hypertension, vasculitis (fever, rash, bowel problems), meningitis (fever, stiff neck), cerebral venous thrombosis (personal or family history of hypercoagulable states, smoking, oral contraceptive pills), and medications that may cause high intracranial pressure (ICP), such as tetracyclines, vitamin A and derivatives, lithium, steroids, or steroid withdrawal, should all be included in the history questions [1].

Risk factors

Recent weight gain, thyroid disease, anemia, polycystic ovarian syndrome, and obstructive sleep apnoea are the potential risk factors for papilledema.

Clinical examination

A thorough neuro-ophthalmic examination and an immediate blood pressure check will be part of the physical examination to rule out malignant hypertension. A normal afferent visual function, which includes normal color vision, normal best-corrected visual acuity,

absence of a relative afferent pupillary defect, and normal confrontation visual fields (aside from an enlarged blind spot), is frequently observed alongside the bilateral optic disc swelling observed on the fundus exam. An Optical coherence tomogram (OCT) of the macula is helpful in this situation if central vision is lost without loss of the peripheral visual field and if there is no relative afferent pupillary impairment. This indicates that the fluid may have extended into the macula and caused macular edema [1].

Fundus examination

Variable symptoms might be discovered according to how serious the illness is:

1. The optic nerve head: opacification of the retinal nerve fibers, border elevation, hyperemia, and cup obliteration (Figure 1a and 1b).
2. Venous dilatation, vascular tortuosity, hemorrhages, cotton wool patches, and exudates (which can extend to the macula, creating a macular star appearance) are vascular characteristics associated with congestion (Figure 1c and 1d).
3. Mechanical characteristics include choroidal folds from posterior globe deformation and retinal folds (such as peripapillary circumferential water marks known as Paton's lines) (Figure 1e and 1f).
4. Because of gliosis-the greying of the retinal fibers as a result of scarring-optic disc pallor and decreasing swelling are possible symptoms of chronic papilledema. Optociliary shunts may also be present [12].

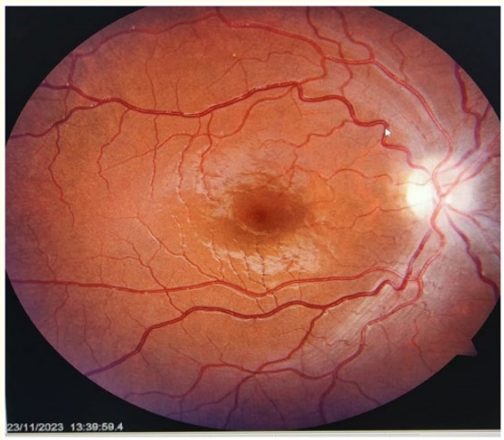

Figure 1a: *Grade 1 papilledema.*

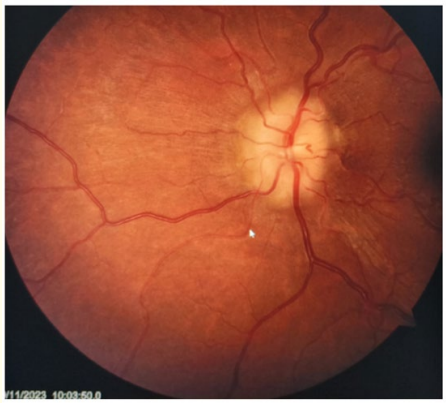

Figure 1b: *Grade 2 papilledema.*

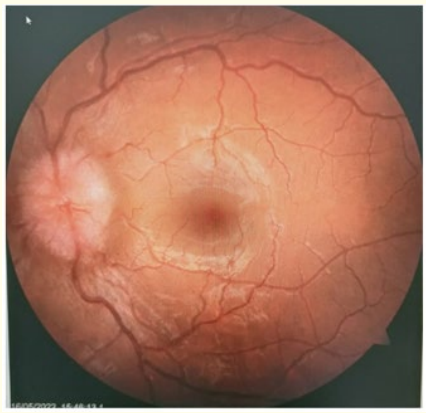

Figure 1c: *Grade 3 papilledema.*

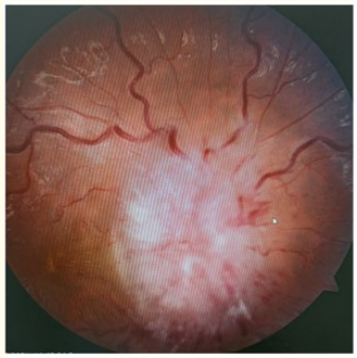

Figure 1d: *Grade 4 papilledema.*

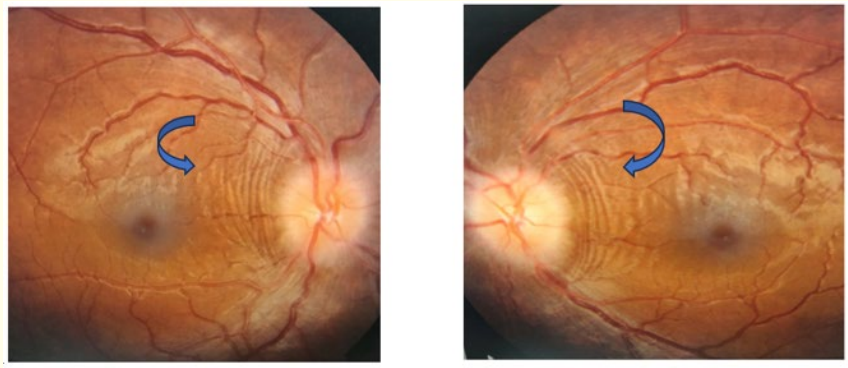

Figure 1e and 1f: *Paton's fold.*

A reliable inter-observer grading technique proposed by ophthalmologist Lars Friesen is routinely used when the disc edges become blurry. The grading is shown in table 1.

Grade 1	The normal temporal boundary and nasal border of the optic disc are blurred, and the typical radial arrangement of nerve fiber bundles is also disturbed.
Grade 2	Increased nasal and temporal (circumferential) blurring of the optic disc compared to grade 1.
Grade 3	All boundaries are obscured. the optic nerve head's diameter has increased. one or more major blood artery segments exiting the disk are obstructed. Finger-like extensions on the peripapillary halo-irregular outer fringe.
Grade 4	Raising the nerve head in its entirety. obscuring all boundaries. halo surrounding the periphery. complete darkness on a main blood artery segment's disc.
Grade 5	Dome-shaped projections that show how the optic nerve head has expanded anteriorly. The peripheral halo is smooth and narrowly defined. A section of a major blood vessel is completely obscured. The optic cup is destroyed.

Table 1: *Friesen grading.*

Etiology of papilledema

In adults, normal ICP is usually less than 250 mm of water; in children, it is typically less than 280 mm of water. The most frequent cause of papilledema is idiopathic intracranial hypertension (IIH). Other causes include craniosynostosis (small skull), space-occupying lesions from tumors or hemorrhages, or brain edema from blunt head trauma (Table 2). Additionally, obstructions of the flow of cerebrospinal fluid (CSF) can occur from meningitis, cerebral venous thrombosis, reduced absorption of CSF, and increased production of CSF (choroid plexus papilloma) [13].

Space-occupying lesions	Intracranial mass (Craniopharyngioma) Abscess Hemorrhages Arteriovenous malformation
Focal or diffuse cerebral edema	Trauma Toxic Anoxia
Reduction in size of the cranial vault	Craniosynostosis Thickening of skull
Blockage of CSF flow	Non-communicating hydrocephalus
Reduction in CSF reabsorption	Communicating hydrocephalus Meningitis Elevated cerebral venous sinus pressure Elevated CSF protein
Increased CSF production	
Idiopathic intracranial hypertension	

Table 2: *Causes of increased intracranial pressure.*

IIH

Primary pseudotumor cerebri is another name for it. IIH may be seen in any gender or age group but has a high predilection for females of childbearing age, especially when coupled with obesity. While males are less frequently affected, constituting less than 10% of adult IIH patients, the affected population also tends to be obese and is more likely to sustain a worse visual prognosis compared to their female counterparts. Daily headaches, pulse-synchronous tinnitus, momentary visual obscuration, and papilledema with concomitant vision loss are typical presentation symptoms for the patient. IIH was shown to have an incidence of 0.9 to 1.0 per 100,000 in the general population, 1.6 - 3.5 per 100,000 in women, and 7.9 - 20 per 100,000 in women who were overweight [14].

Certain systemic conditions, such as uremia, hypothyroidism, Addison disease, Behçet's syndrome, polycystic ovary syndrome, coagulation abnormalities, and obstructive sleep apnea, have been linked to IIH along with other potential risk factors. There is still much to learn about the underlying mechanics of these connections. Apart from systemic diseases, some drugs such as cyclosporine, tetracyclines, lithium, vitamin A, anabolic steroids, oral contraceptive pills, and nalidixic acid have also been linked to IIH.

IIH is a diagnosis of exclusion usually made with modified Dandy criteria. These criteria include normal neuroimaging (usually magnetic resonance imaging, preferably with and without contrast, and magnetic resonance venogram); signs and symptoms due only to high ICP (headache, pulse-synchronous tinnitus, papilledema, and diplopia due to a non-localizing sixth nerve palsy) (Table 3) [14].

Symptoms and indicators of elevated ICP or papilledema, if any
High ICP measured in the lateral decubitus posture with documentation
Normal CSF composition
For typical patients, MRI and magnetic resonance venography (MRV) is normal; for all other patients, MRI and contrast-enhanced CT
No additional reason for a higher ICP

Table 3: *Modified Dandy criteria [14].*

In the past three years, there has been a tremendous amount of published research on IIH, especially from the idiopathic intracranial hypertension treatment trial (IIHT) [15].

IIHT

- Acetazolamide when used in IIH patients with mild visual loss produces a modest improvement in PMD (Perimetric mean deviation) over six months. The improvement is much greater in subjects with moderate to high-grade papilledema.
- Acetazolamide has the greatest effect on visual field function and papilledema in the first month of escalating dosage.
- Acetazolamide-plus-diet patients lost twice as much weight as placebo-plus-diet patients but the acetazolamide effect on PMD (Perimetric mean deviation) was independent of the weight loss.
- The improvements in the visual field, neck discomfort, pulsatile tinnitus, and dizziness/vertigo that outweighed the side effects of acetazolamide appeared to be the primary mediators of the positive effects of the medication on quality of life.

Recent advances in IIH: OCT

A non-invasive technique for high-resolution (micron scale) imaging of the optic nerve and retinal microstructure is OCT.

CSF pressure-lowering therapies have been demonstrated to alter the subsurface shape of the peripapillary retinal pigment epithelium/basement membrane junction, as measured by OCT. This may indicate a structural alteration in IIH associated with papilledema. Moreover,

alterations in the optic nerve head volume and peripapillary retinal nerve fiber layer have a strong correlation with papilledema grade changes.

About 40% of IIH patients have choroidal creases and folds, which are a common accompaniment to papilledema. Using fundus images and OCT, Sibony., *et al*. have examined choroidal folds in IIHTT participants.

Space occupying lesion

A mass lesion's rise in intracerebral volume may cause a high ICP and papilledema, although, in chronic situations, compensatory mechanisms may prevent papilledema from developing. Only 28% of patients aged 0 to 90 years who had a history of brain tumors and presented to an emergency room in one series had papilledema [16]. On the other hand, papilledema was discovered in up to 60% - 80% of patients with brain tumors in a few larger neurosurgical studies [17].

Compared to supratentorial mass lesions, infratentorial mass lesions are more prone to cause papilledema because they may impede the ventricular outflow at the relatively thin Sylvian aqueduct. Children's brain tumors typically occur in the posterior fossa, which is why papilledema is a common symptom [18].

Craniopharyngioma (CP)

A rare and slowly developing brain tumor, childhood craniopharyngiomas are frequently found in the sellar and suprasellar regions on imaging (Figure 2). Visual impairment, visual field defects like homonymous hemianopias (Figure 3), elevated ICP and hypothalamic and/or pituitary deficits are common manifestations. The seller and/or suprasellar regions of the brain are frequently the site of CP. The annual incidence of cerebral palsy ranges from 0.5 to 2.0 new cases per million individuals, with a bimodal distribution in children aged 5 - 14 and adults aged 50 - 74 [19-22].

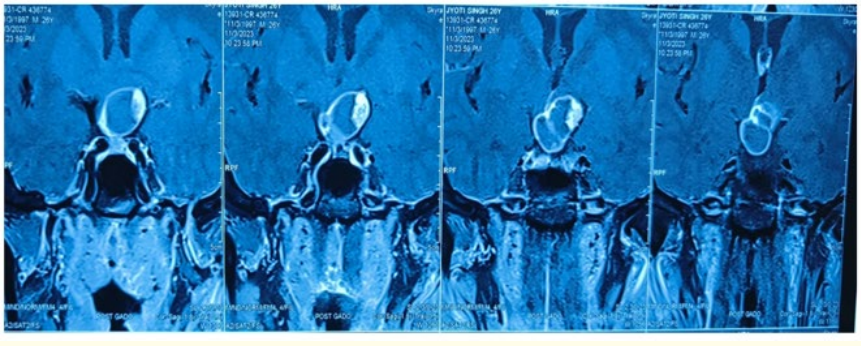

Figure 2: *Craniopharyngioma in T1 weighed MRI brain.*

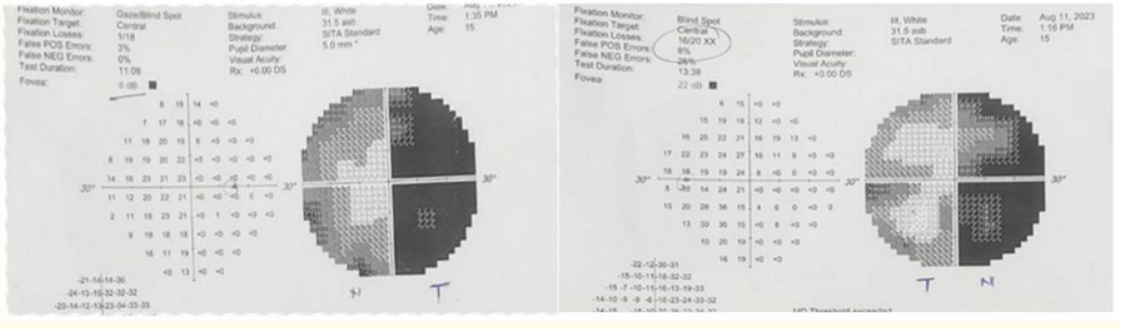

Figure 3: *Homonymous hemianopia.*

Cerebral hemorrhage

Subarachnoid hemorrhage (SAH), Intraparenchymal hemorrhage (IPH), and acute subdural hematoma (SDH) can all occur hours after the hemorrhage and are all potentially linked to papilledema. Even when the ICP is high, only a small percentage of individuals experience papilledema as a result of SAH or IPH. Just 16% of patients in a group of patients with ruptured aneurysms had papilledema despite having SAH [23]. Age, sex, or the location of the aneurysm were unrelated to the prevalence of papilledema in SAH. It is thought that SAH causes papilledema by obstructing either CSF absorption at the arachnoid granulations or CSF outflow inside the ventricular system. Similarly, several researchers have shown that 10% - 24% of individuals with aneurysmal SAH have papilledema [24].

Trauma

Apart from SAH, SDH, IPH, and epidural hematoma, trauma can also result in elevated ICP and papilledema through different pathways. Only 3.5% of patients in research involving severe head injuries exhibited papilledema, which showed minimal association with the severity of high ICP [24]. Therefore, elevated ICP in these patients is not always ruled out even in the absence of papilledema. Patients who experience head trauma typically get modest (albeit highly variable) papilledema, which might appear right away, a few days later, or even up to two weeks later.

Meningitis

Meningitis can result in obstructive hydrocephalus, severe secondary cerebral edema, or decreased CSF absorption due to inflammation at the arachnoid granulation level, all of which can raise ICP. Meningitis has been associated with papilledema only rarely, and when it does occur, it usually manifests as mild, temporary papilledema that varies greatly. In one study of 2,178 cases of meningitis, only 2.5% of patients had papilledema [25] and other larger older series of syphilitic meningitis showed a similar incidence of papilledema [26].

Hydrocephalus

Another cause of elevated ICP and consequent papilledema is obstructive (non-communicating) hydrocephalus, which arises from compression of the ventricular system or its related foramina. Neoplasms, intraventricular or SAH, meningitis and congenital aqueductal stenosis are a few common causes of hydrocephalus [27].

Spinal cord lesions

An uncommon cause of elevated ICP that might lead to the development of papilledema is a spinal canal tumor. While extradural spinal tumors can also result in elevated ICP, intradural spinal tumors account for the majority of these cases [27,28].

More than half of the spinal cord lesions linked to papilledema are either neurofibromas or ependymomas, and they typically occur in the lumbar and thoracic areas.

In these circumstances, the source of the elevated ICP and papilledema is most likely reduced CSF absorption as a result of increased CSF protein produced by this and other tumors blocking the arachnoid granulations. Guillain-Barré syndrome patients may experience papilledema due to a similar mechanism [29].

Obstruction or impairment of intracranial venous drainage

A blockage (such as thrombosis) of cavernous sinus (CVS) drainage can cause papilledema and elevated ICP without ventricular enlargement and with otherwise normal CSF. The obstruction is caused by compression or thrombosis of the CVS, primarily affecting the transverse (lateral) and superior sagittal sinuses [30]. When there is septic thrombosis of the CVS, papilledema usually develops early, is bilateral and is symmetrical. Both adults and children's CVS can develop aseptic thrombosis; the superior sagittal sinus is more commonly impacted [30]. These patients may be predisposed to the use of oral contraceptives, have systemic conditions such as renal

disease, pregnancy, or cancer, or have systemic inflammatory or infectious diseases such as systemic lupus erythematosus, Behçet disease, trichinosis, or sarcoidosis. Additionally, these patients may have an underlying coagulopathy such as Factor V Leiden mutation, prothrombin, activated protein C resistance, protein C, S, or antithrombin III deficiency, anticardiolipin antibodies, or hyperviscosity syndromes.

Anomalies of cranium

Patients with premature synostosis of the cranial sutures may experience papilledema in as many as 12% - 15% of cases. Patients with certain craniofacial dysostosis (Crouzon syndrome) or acrocephalosyndactyly (Apert syndrome) have an up to 40% increased incidence of papilledema [31]. According to earlier research, up to 50% of patients with papilledema and craniosynostosis subsequently experienced blindness in both eyes or a substantial decrease in vision. Patients may also show papilledema and secondary IH if they have a reduced posterior fossa volume and the Chiari malformation.

Diagnosis

Investigations can include ophthalmic, neuro-imaging, and a lumbar puncture.

Ophthalmic investigations

- An objective use of the Spectral domain for OCT of the RNFL (SD-OCT RNFL) may be to detect modest disc enlargement and track improvement in the condition [32]. OCT of the inner plexiform layer (GCL-IPL) of ganglion cells is more accurate in differentiating between atrophy and enhanced thickness brought on by treatment response [33].
- Severe persistent papilledema may show signs of progressive peripheral field loss, which may eventually spread to the central nervous system.
- Unlike disc staining without leakage in pseudo papilledema, fluorescein angiography can identify disc leakage in cases of real optic disc edema. Furthermore, pseudo papilledema (such as optic disc drusen) may be visible on autofluorescence or B scan ultrasonography as well as increased depth imaging OCT of the optic nerve head.

Neuroimaging

When paired with a CT venogram, the immediate goal of an urgent CT scan would be to rule out a space-occupying lesion, and in the right situation, it would also rule out cerebral venous thrombosis. Additionally, if meningitis was suspected, an MRI or MRV with contrast would evaluate leptomeningeal enhancement and look for signs of elevated ICP. The following are neuroimaging characteristics of high ICP [34]:

- A partially or empty sella.
- Prominent CSF and dilated perioptic nerve sheath.
- Tortoiseness of the vertical or horizontal optic nerve.
- The globe flattening posteriorly. It is possible to observe an intraocular optic nerve protrusion in cases of significant optic disc edema.
- Tonsillar ectopia is a significant finding to watch for in patients with papilledema, as depending on its severity, these individuals may be at risk of herniation during the LP.

Lumbar puncture

- Note the opening pressure and composition of the CSF (avoid neoplastic, viral, and inflammatory causes).
- Getting opening pressure, glucose, protein, differential, and cell count are among the minimal needs.

Management

The objectives of management are to address the underlying cause, preserve vision, and relieve symptoms (Table 4).

Etiology of papilledema	Treatment
Space-occupying mass, Chiari malformation, or hydrocephalus	Surgical treatment
Secondary causes	Directly treating the underlying cause
Cerebral venous sinus thrombosis	Examine the underlying reason. Include anticoagulation
Potential contributing factors	Eliminate any influencing factors.
IIH with symptoms and visual loss	Weight loss and diet, diuretics
IIH with failed maximal medical therapy	Consider a surgical substitute.

Table 4: *Etiology-based management options.*

Medical management

The cornerstone of medical treatment for IIH is medication along with nutrition and weight loss. A reduction in body weight of 5% - 10% is typically necessary to see an improvement in symptoms and indicators [35].

Patients with IIH who were given a 425-calorie diet per day for three months saw a decrease in CSF pressure, according to Sinclair., *et al*. patients with IIH should undergo screening for obstructive sleep apnea and receive the necessary treatment.

For IIH patients experiencing mild to severe vision loss, acetazolamide, an inhibitor of carbonic anhydrase, in conjunction with a low-sodium weight-reduction diet, is a commonly used first-line combination.

Topiramate is used to treat primary headache disorders, including IIH. Topiramate and acetazolamide were found to be equally effective in treating mild to moderate IIH in a single small randomized treatment trial. Topiramate is not recommended as our first-line treatment for IIH due to potential neurocognitive side effects [36].

Although long-term use of steroids to lower ICP is not advised because of the risk of rebound IIH after withdrawal, they were historically widely used to treat IIH [37,38].

Serial lumbar punctures may be taken into consideration for patients who require repeated short-term temporizing measures to lower CSF pressure while awaiting a definitive surgical treatment or medicinal improvement, but who are pregnant or not suited for medical therapy (cryptococcal meningitis) [39].

Surgical management

Patients who show substantial vision loss at presentation, acute fulminant IIH, or progressive vision loss despite optimal medical therapy, necessitate surgical procedures [40,41].

The surgical alternatives include venous sinus stenting, CSF diversion (e.g. lumboperitoneal shunt [LPS] or ventriculoperitoneal shunt [VPS]), and ONSF (Optic nerve sheath fenestration).

Prognosis

The chronicity of papilledema affects the prognosis of the condition. An extended period of elevated ICP may cause a permanent loss of the nerve fiber layer, which may lead to progressive loss of central visual acuity and visual field.

Complications

If the underlying ICP is not appropriately treated, complications may occur. This non-treatment may be the consequence of misdiagnosed excessive ICP or failed surgery. Failure of CSF shunts can result from malfunction, blockage, or blockage, and failure of optic nerve sheath fenestration can happen as a result of scarring that follows. Severe infection is a risk associated with any form of surgery, but it is especially high when the CSF space is accessed [42].

Summary

The eye care specialist should be knowledgeable in taking a relevant history and physical, as well as how to evaluate and look at the optic disc. Prioritizing a prompt workup and making the right specialist referrals are important. Precise and effective communication between co-managing and referring healthcare providers optimizes patient care and safety. For instance, when an ophthalmologist notices that IIH requires surgery, they should consult with neurosurgery to determine the best course of action. When risks, advantages, and choices from several disciplines are communicated to the patient, the patient's autonomy is also maintained.

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