Literature Review

Neuro-opthalmological and neuro-surgical aspects of papilledema

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Papilledema is optic disc swelling that is secondary to elevated intracranial pressure. Possible conditions causing high intracranial pressure and papilledema include brain neoplasms, head trauma, hydrocephalus, and other disorders of the central nervous system. Papilledema is diagnosed using ophthalmoscopy and/or neuroimaging. The differential diagnosis includes pseudopapilledema and inflammatory and vascular disorders of the optic disc. The treatment is aimed at reducing the intracranial pressure of the patient.

Keywords:
papilledema, intracranial hypertension, optic disc

The evaluation and management of papilledema is an integral part of neuro-ophthalmology, a subspecialty that focuses on the eye and its relationship to the central nervous system. Papilledema is non-inflammatory optic disc swelling that is secondary to elevated intracranial pressure (ICP) in the presence of compression or obstruction of the cerebrospinal fluid pathways or the development of a space occupying pathological process in the cranial cavity [1]. The subarachnoid space is continuous with the optic nerve sheath. Hence, as the ICP increases, the pressure is transmitted to the optic nerve, and papilledema develops. It is noteworthy that optic disc swelling in general includes both an eye disease with optic disc changes and signs of intracranial hypertension [2, 3]. Optic disc edema in raised intracranial pressure was first described in 1853, independently, by Türck and by Coccius [4]. Von Graefe in 1850 [5] defined it as a "state due to increased pressure within the cranium", called it Stauungspapille (choked disc), and reported his observations in patients with brain tumor and swelling of the optic nerve disc. The word "papilledema" was first used in 1908 by Parsons to replace von Graefe's term, Stauungspapille, caused by intracranial hypertension (ICH). No differentiation has been reported between papilledema and other types of optic disc swelling until the 1900s [6].

Optic disc swelling is a challenging presentation with a wide differential diagnosis including papilledema, papillitis, anterior ischemic neuropathy and other optic nerve diseases. If the fundus shows signs of papilledema, early differential diagnosis is mandatory and the patient should be urgently referred to subspecialists.

It is important to remember that although papilledema cannot develop without ICH, case reports do exist of ICH without papilledema [7]. Initially, acute development of intracranial hypertension (head injury with intracerebral hemorrhage, subdural hematoma, and cerebral aneurysm rupture) is not accompanied by choked disc. Patients with chronic intracranial hypertension secondary to brain tumor most commonly show fundus signs of hypertension [3].

The brain is enclosed in the craniovertebral cavity that is filled with the brain tissue (80%), cerebrospinal fluid (10-15%) and blood (5%) [8]. A change in ratios of these components will result in imbalance and increased ICP. The potential mechanisms of elevated ICP include effects of the following: a space occupying process within a portion of the cranial cavity; local or diffuse brain swelling; low intracranial volume (thickened skull

bones); impaired SCF flow through the ventricular system (occlusive hydrocephalus) or arachnoidal granulations (communicating hydrocephalus); altered CSF resorption due to impaired intra- or extracranial venous flow; and increased CSF production [5].

The most common causes of ICH are as follows [5, 10, 11]: (1) space occupying lesions of the brain and spinal cord (neoplasms; intracerebral, subdural, or epidural hematomas and subarachnoidal hemorrhage; brain swelling; arteriovenous malformations; abscesses and parasitic diseases); (2) blocked ventricular system (occlusive hydrocephalus associated with inflammatory, tumor-related or congenital aqueduct stenosis; Arnold-Chiari malformation); (3) altered CSF production or resorption (communicating or nonresorptive hydrocephalus; elevated venous tension associated with arteriovenous fistula or malformation, cerebral sinus thrombosis, inflammatory meningitis or idiopathic ICH); (4) head trauma; and (5) congenitally thickened or defective skull bones.

Papilledema is present in 40% to 80% of cases with brain disorders, with the higher occurrence in patients with brain neoplasms. Thus, in 1968, Tron reported papilledema in 70.7% of patients with brain tumors, the high percentage being attributed to the absence of MRI or CT in the 1960s. More recently, Eliseieva found papilledema in 30% of patients with brain tumors. As compared to benign tumors, patients with malignant brain tumors have a significantly higher risk of papilledema, because a rapid infiltrative growth and perifocal or diffuse brain edema are characteristic for malignancies [12-14]. Neuro-ophthalmic symptomatology (visual field loss, changes in the fundus and oculomotor alterations) often depends on the location of the lesion [15]. The malignancy, midline brain location of the space-occupying lesion and intracerebral extension of the tumor are the factors affecting the occurrence and severity of papilledema in brain lesions [9]. Another factor affecting the occurrence of papilledema is patient age. Others have reported that papilledema was more common in patients younger than 60 years [16] and 3 to 30 years [5], which was attributed to a low reserve capacity of the craniovertebral contents.

A choked optic disc is seen in a fifth of patients with occlusive hydrocephalus (altered CSF circulation) and in less than a tenth of patients with non-occlusive hydrocephalus (altered CSF resorption) [9]. In addition, papilledema was found in 22% of patients with encephalitis or meningitis. Meningites and encephalites result in diffuse brain edema, occlusive hydrocephalus and/or adhesive process. Moreover, papilledema was found in 25% of patients with cerebrovascular disorders. Cerebral aneurysms manifest themselves by subarachnoidal hemorrhage and brain edema, whereas arteriovenous malformations alter CSF resorption by arterial blood shunting to the cerebral venous system [5].

Papilledema develops in the fundus in 15% of patients with severe head trauma. This is associated with massive hemorrhages, intracellular, subdural or epidural hematomas and local or diffuse brain swelling [17].

Papilledema is seen in almost all patients with idiopathic intracranial hypertension. This condition is characterized by increased CSF pressure and development of papilledema in the absence of a space occupying lesion in the cranial cavity or changes in CSF composition. Of note is that intracranial hypertension manifests itself by visual abnormalities in 50-70% of patients [9].

Pathogenesis

A change in CSF dynamics or emergence of an intracranial lesion results in a raised intracranial pressure. The orbital portion of the optic nerve communicates with the submeningeal space [18]. Intracranial hypertension raises the CSF pressure in the subdural space of the optic nerve, resulting in increased tissue pressure in the optic nerve, impaired slow component of axoplasmatic transport and optic disc axon swelling. In addition, there is altered central retinal venous flow [4, 9].

Classification

The ophthalmoscopic picture of the fundus is the main diagnostic criterion for the classification of papilledema. In the post-Soviet countries, the most commonly used classification scheme is that by Tron (1968) which distinguishes the following stages of papilledema: early, marked, full-blown, and atrophic stages, and post-papilledema optic atrophy. Complicated papilledema (i.e., papilledema with the involvement of various sites of the visual pathway into the pathological process) is separately distinguished [13]. The classification by Serova [5] may be considered as a modified version of the classification by Tron and distinguishes the following stages of papilledema: early, moderate, marked, and regressive stages and secondary atrophy.

The classification by Jackson describes the disc appearance according to the duration of papilledema: (a) early; (b) fully developed; (c) chronic; and (d) atrophic [11].

Complicated papilledema (i.e., papilledema with the involvement of various sites of the visual pathway into the pathological process) is separately distinguished [19]. There are five main signs of complicated papilledema: (1) the visual field changes (hemianopia) unusual for uncomplicated papilledema; (2) high visual acuity in the presence of significant visual field changes; (3) a substantial difference in visual acuity between eyes; (4) a substantially reduced visual acuity without atrophic changes; (5) bilateral pupilledema with unilateral atrophic changes [13, 19].

Complicated papilledema may develop in one of the following three ways: (1) the pathological process causes increased ICP and then affects the visual pathway; (2) the pathological process simultaneously increases the ICP and affects the visual pathway; (3) the pathological process affects the visual pathway and then increases ICP [19]. The intracranial portion of the optic nerve and chiasm

are located on the basal surface of the brain and may be involved in the pathological process in the brain.

In the Foster Kennedy syndrome, patients develop optic atrophy in one eye and papilledema in the other eye. Initially, the pathological process compresses the intracranial portion of the optic nerve and primary atrophy develops. As the process progresses, the ICP raises and papilledema develops in the fellow eye [1, 16].

In the pseudo-Foster Kennedy syndrome, patients develop optic atrophy in one eye and papilledema in the other eye, but no intracranial injury develops. The condition is associated with idiopathic intracranial hypertension and is accompanied by raised ICP. About 25% are asymptomatic and are revealed during routine eye examination [20, 21].

In most cases, papilledema is diagnosed on the basis of the ophthalmoscopic picture of the fundus and presence of various grades of optic disc swelling which is manifested by hyperemia, blurred optic disc margins and blurred cup margins, full retinal veins and absence of spontaneous venous pulse. However, if these signs are incipient, they may be a variant of the norm or related to other pathology. Congenital optic disc abnormalities may masquerade as early papilledema, and the former should be differentiated from the latter [22]. The normal color of the optic disc varies and depends on the state of the capillary network. The optic disc tends to be hyperemic in hyperopes, whereas myopes have whiter appearing optic discs.

The absence of spontaneous venous pulse in the fundus may be an important sign of early ICH. The spontaneous retinal venous pulse is present in 85-99% of practically healthy individuals and disappears with raised ICP. However, others do not consider this sign important because the spontaneous retinal venous pulse is present not in all normal individuals [12, 17, 23]. Studies of the spontaneous retinal venous pulse are reasonable for early diagnosis in emergency settings when general condition of the patient is serious (head trauma, cerebral aneurysm rupture).

Establishing a diagnosis of papilledema requires attention to patient's general complaints. Headache, nausea, sinus bradycardia, oculomotor nerve paresis, and epileptic seizures are symptoms of hypertensive hydrocephalus syndrome [16, 19]. In addition, episodes of transient obscuration of vision may occur. These conditions are associated with large fluctuations in ICP, transient impairment of optic nerve circulation and compression of nerve fibers by edema [11, 24]. The episodes of transient obscuration of vision may occur up to 20–30 times a day, and are often precipitated by postural changes (particularly from a bent-over position) or head rotation.

Moderate papilledema is characterized by increased disc swelling (hyperemia, blurred disc margins, and optic nerve cupping). In addition, the retinal veins are dilated, tortuous and hidden in the swollen tissue, and hemorrhages and white foci of transudation appear in the retina surrounding the optic nerve.

Marked papilledema is characterized by an abrupt increase in disc elevation, increase in disc diameter, marked venous dilation, and numerous hemorrhages and focal exudates on the disc and in the peripapillary region. When papilledema persists, the ophthalmoscopic picture certain changes. The initial disc hyperemia changes to pallor, which is associated with decreased caliber and number of the optic disc vessels and substitution of normal optic disc fibers with the glial tissue. Optic atrophy secondary to papilledema develops [1, 10, 13, 19, 20].

The important issue is how long patients have papilledema without visual deterioration. It is known that patients with papilledema have their visual function maintained for some time. Visual acuity may be not deteriorated (excluding transient obscurations of vision) even in moderate or marked papilledema. A visual disorder most commonly develops between 1 month and 5 years after the onset of papilledema [12]. The time from the onset of papilledema to the onset of secondary optic atrophy depends on numerous factors including the severity of intracranial hypertension and whether the latter is transient or not. Atrophic changes may develop several weeks or days after the finding of papilledema, especially when ICP increases rapidly. Rapid deterioration of visual field acuity has been observed in patients with venous sinus thrombosis. It has been reported that, in some patients, the visual loss progressed to complete loss of vision within 1-2 weeks of onset of initial symptoms [19]. Rapid development of papilledema results in increased damage to optic nerve fibers, and, consequently, more severe visual abnormalities. Papilledema-associated visual abnormalities are attributed to compression or ischemia of nerve fibers due to swelling.

The following four pathogenetic components of the deterioration of visual acuity and fields in patients with papilledema have been identified [9, 12]: (1) blind spot enlargement attributed to compression and mechanical displacement of the peripapillary retina by the swollen disc; (2) concentric peripheral visual field constrictions attributed to compression or ischemia of nerve fibers in the scleral canal due to swelling; (3) a decrease in central vision at the stages of marked papilledema and secondary atrophy attributed to ischemic damage to the papillomacular bundle, and swelling and dystrophic changes in the central retina; (4) the process of nerve fiber atrophy initiates at the level of the scleral lamina cribrosa in marked papilledema.

Vision loss from optic neuropathy can develop immediately after ICP has been normalized or months to years later, long after papilledema has disappeared. The immediate type of visual loss has been amply documented in patients who undergo surgery for brain tumor or CSF diversion for high ICP. Such patients have always had evidence of atrophic papilledema, before the decompressive procedure occurred. The explanation for this "postdecompression optic neuropathy" is uncertain. Perhaps tumor decompression and restoration of normal ICP disturb compensatory blood flow to the optic nerve [3].

Changes in visual fields are characteristic for papilledema. Visual field examination is the most informative for identification of visual impairment [25, 26].

Blind spot enlargement appears before ophthalmoscopic signs develop, and is therefore an early sign of ICH. Fedorov paid attention to it as early as the 1950s [1]. This symptom is the most common and may remain the only visual field defect for long. Enlargement of the blind spot in papilledema is secondary to mechanical displacement of the peripapillary retina by the swollen disc. Subsequently, visual field defects may vary and may include concentric visual field constriction, loss of the inferonasal visual field, nasal visual field defects, and arcuate, central, cecocentral and paracental scotomas [25, 26].

Heidelberg retina tomography (HRT) and optical coherence tomography (OCT) are essential diagnostic modalities that enable to identify and quantify papilledema through the measurement of cup depth and to monitor the efficacy of treatment interventions. The true disc edema coefficient (TDEC) represents the ratio between the ophthalmoscopically nonvisible edema, that is the space included between the planes of inner retina and lamina cribrosa (measurable as US-HRT), equivalent to the preexisting optic disc cup filled by the nerve fiber swelling, and the total height of the disc edema ultrasonographically measured: TDEC = (US-HRT)/US [27]. OCT does not appear to differentiate between individuals with pseudopapilledema and those with mild papilledema caused by increased ICP [28]. However, whole image and nasal peripapillary sector capillary densities using optical coherence tomography angiography (OCT-A) have diagnostic accuracy for differentiating true and pseudo-disc swelling [29, 30]. Fluorescein angiography (FA) of the optic nerve identifies early optic nerve swelling which is reflected in the extravasal leakage of fluorescein during circulation of the dye in retinal vessels and increased disc fluorescence. Optic nerve ultrasonography enables assessment of disc cupping and state of the subdural space of the orbital portion of the optic nerve. The enlarged subdural space of the optic nerve is seen in patients with ICH. The method is helpful in differentiating optic disc drusen from papilledema [31, 32].

Papilledema classically presents as bilateral swelling of the optic nerve disc, with well-preserved visual acuity; however, the presence of other signs of hypertensive hydrocephalus syndrome (headache, transient obscurations of vision) requires urgent neuroimaging evaluation and neurological/neurosurgical consultation. If there is no brain MRI or CT evidence of changes, it is required to exclude idiopathic intracranial hypertension. In addition, MR venography and MR angiography should be performed to exclude venous sinus thrombosis and arteriovenous fistula, respectively [2, 12].

Papilledema should be differentiated from pseudopapilledema and other types of optic disc swelling. Pseudopapilledema may be caused by congenital optic disc elevation (crowded optic disc) and is not an uncommon finding in children. The diagnosis may be aided by serial dilated fundus examinations; pseudopapilledema will be stable over time, while untreated papilledema might change. Optic disc drusen is another cause for pseudopapilledema. Deeper drusen are especially difficult to differentiate from papilledema. Occasionally, true papilledema may coexist with optic disc drusen [33]. Patients with glial hyperplasia (myelinated fibers), hypermetropic refractive errors, vitreopapillary traction and Bergmeister papilla may exhibit ophthalmoscopically blurred disc margins, and these conditions may ophthalmoscopically mimic papilledema. Ischemic edema of the optic nerve or disc develops in anterior ischemic optic neuropathy, central retinal vein thrombosis, hypertonic neuropathy, and diabetic papillopathy. Inflammatory optic nerve edema is seen in inflammatory processes in the optic nerve (optic neuritis, neuroretinitis). Toxic damage to the optic nerve caused by ethambutol, linezolid, amiodarone or methanol is sometimes accompanied by optic disc edema and hyperemia, especially in the early stages of toxic optic neuropathy. Leukemia and metastatic process may be reflected by optic disc edema through the development of leukemic and metastatic infiltration of the optic nerve [9, 32, 34-40].

Treatment

Since is the main cause of papilledema is an increased ICP, treatments should be aimed at decreasing the ICP. Hence, intracranial lesions and hemorrhages should be removed, cerebral aneurysms stented, and CSF diversion and/or a series of lumbar punctures done. Carbonic anhydrase inhibitors are additionally administered to patients with idiopathic intracranial hypertension. Optic nerve sheath fenestration has been proposed to decrease CSF pressure in the subdural space of the optic nerve [41]. The outcome may be doubtful in optic nerve atrophy secondary to pupilledema, and, naturally, the methodology is more helpful in the absence of signs of optic nerve atrophy secondary to pupilledema. Reduced visual acuity, progressive visual field constriction, and presence of marked papilledema are indications for urgent surgery for decreasing ICP [8].

Papilledema is a symptom of ICP and is frequently associated with a serious brain disease. Establishing a correct diagnosis requires from the ophthalmologist not only attention to the ophthalmoscopic changes of the fundus, but also identification of general symptoms of hypertensive hydrocephalus like transient obscurations of vision, headache, and nausea. Since papilledema is a symptom of decompensation of the pathological process, early differential diagnosis is mandatory, and the patient should be urgently referred to the subspecialist. Neurologists, ophthalmologists and neurosurgeons participate in the diagnosis, treatment and longitudinal monitoring of patients with this disorder. A multidisciplinary approach for and early detection of papilledema in some cases allows saving not only vision, but lives as well.

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