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Traumatic Optic Neuropathy: A Review and Update on Investigations and Management by Asia Pacific Ophthalmic Trauma Society

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Abstract

Traumatic optic neuropathy (TON) is defined as damage to the optic nerve resulting in loss of visual function that cannot be explained by other ocular pathology. Mechanisms of TON can be classified into “direct” or “indirect”. Investigation of TON via various imaging modalities has been reported. The management and appropriate timing of intervention of indirect TON has been much debated. To date, there is insufficient evidence and guidance in determining the most appropriate treatment. In this review, we summarize the clinical features and investigations, and propose a guideline for the management of TON.

Keywords: Traumatic optic neuropathy • Methylprednisolone • Surgical decompression

Introduction

The optic nerve is a white matter tract which transmits nervous impulses from the retina to the brain. It consists of axons of retinal ganglion cells and support cells. Surrounding the optic nerve, from deep to superficial, are the pia mater, arachnoid mater, and dura mater. The optic nerve measures approximately 50 mm long and can be divided into four segments: intraocular (1 mm), intraorbital (25-30 mm), intracanalicular (6 mm) and intracranial (5-16 mm).

Traumatic optic neuropathy (TON) is defined as damage to the optic nerve, resulting in acute or subacute loss of visual function that cannot be explained by other ocular pathology. This damage can occur anywhere along the length of the optic nerve.

Literature Review

Epidemiology

The incidence of TON following head trauma ranges from 0.3-5% [1-4]. A prospective 2-year study in the United Kingdom reported a minimum estimated incidence of 1.005 per million [5]. This incidence is similar in the paediatric population [6].

The majority of patients with TON are males in their 20-40s. The leading causes of TON are road traffic accidents, assaults and falls [3,5,7-11]. In the paediatric population, the majority of cases are secondary to falls, road traffic accidents and sports [12,6,13]. Iatrogenic TON can occur as a rare complication of orbital surgeries, endonasal endoscopic sinus surgeries, [12,14,15] or facial fracture repairs [16,17].

Classification

TON can be categorised based on the anatomical location (intraocular, intraorbital, intracanalicular or intracranial) and mechanism of injury (direct or indirect).

Direct injury occurs when there is a penetrating wound that results in partial or complete transection or avulsion of the optic nerve or presence of compressive effects from hemorrhage or orbital emphysema. Indirect TON results from transmission of blunt traumatic force from the surrounding soft tissues or bony structures [18,19].

Direct trauma is more likely to affect the more anterior intraocular and intraorbital optic nerve. The optic nerve is tethered tightly to the globe at the insertion of the optic nerve head, and application of force at this connection point may cause it to be transected. Within the orbit, the nerve may be transected by a sharp object. Other causes of direct TON include optic nerve sheath hemorrhage, orbital hemorrhage and orbital emphysema [20,21].

The intracanalicular and intracranial optic nerve are more susceptible to indirect trauma [22-24,18]. This can be explained by the tight adherence of the intracanalicular optic nerve to the surrounding periosteum [4], shearing of pial vasculature leading to ischemia and intracanalicular hemorrhage, and the close proximity of the intracranial optic nerve to the fixed edge of the falciform dural fold [25].

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Pathophysiology

The pathophysiological basis of primary and secondary impact is paramount in understanding the course and recovery after traumatic optic neuropathy. Though the terminology direct and indirect is commonly accepted, clinically two patterns are observed. Loss of optic nerve continuity due to avulsion, partial or complete transection may develop as a consequence of impaction of missile or bony fragments (Figure 2). This results in "direct primary injury" which is profound and usually irreversible. The degree of optic nerve involvement (partial or complete) influences the vision recovery. Theoretically, early intervention in this situation may reduce the secondary damage to the remaining optic nerve by halting the vicious cycle of ischemia, edema and compression. The second clinical pattern, which is widely recognized as the "indirect" variant, occurs more commonly. A blunt trauma leading to compression and transmission of forces may produce a shear stress on the axons of the optic nerve. In addition, this impact may disrupt the vascular supply of the nerve. These changes lead to axonal stress and "secondary" ischemia, edema, and compression (the vicious cycle). This type of injury is described to be indirect as radiologically there is no disruption of the continuity of the optic nerve. However, in patients presenting with indirect injury, decompression surgery may reveal small fractures of the optic canal with impaction of the bony chips onto the nerve and underlying optic nerve bruising, making the injury "direct or primary" in nature. Thus there may be overlap between direct and indirect injury mechanisms with contribution from both types that may go unrecognized.

We recommend the characterization and quantification of primary and secondary injury in TON. For this, a two-stage model of TON has been proposed (Figure 1). Trauma causes primary irreversible damage to the optic nerve axons at the time of impact. Inflammation and disruption in the vasculature after the impact causes secondary damage. In addition to ischemia resulting from compression of pial vessels supplying the optic nerve, various mechanisms of secondary damage have been suggested, including vasospasm and ongoing edema of the optic nerve (Figure 3) [4]. This compromises the blood supply to any remaining retinal ganglion cells initiating the process of apoptosis leading to loss of these cells [19].

At the cellular level, ischemia and subsequent reperfusion generate oxygen free radicals. These oxygen free radicals can cause lipid peroxidation of polyunsaturated lipids in axonal cell membranes, damaging the neural membrane. Ischemia results in calcium shifting from the extracellular space to the intracellular space. Excess intracellular calcium results in cell death. The coagulation pathway results in production of bradykinin and kallidin, both of which increase free radical production, intracellular calcium production, and arachidonic acid release. Inflammatory cells such as neutrophils and macrophages release enzymes and free radicals [4].

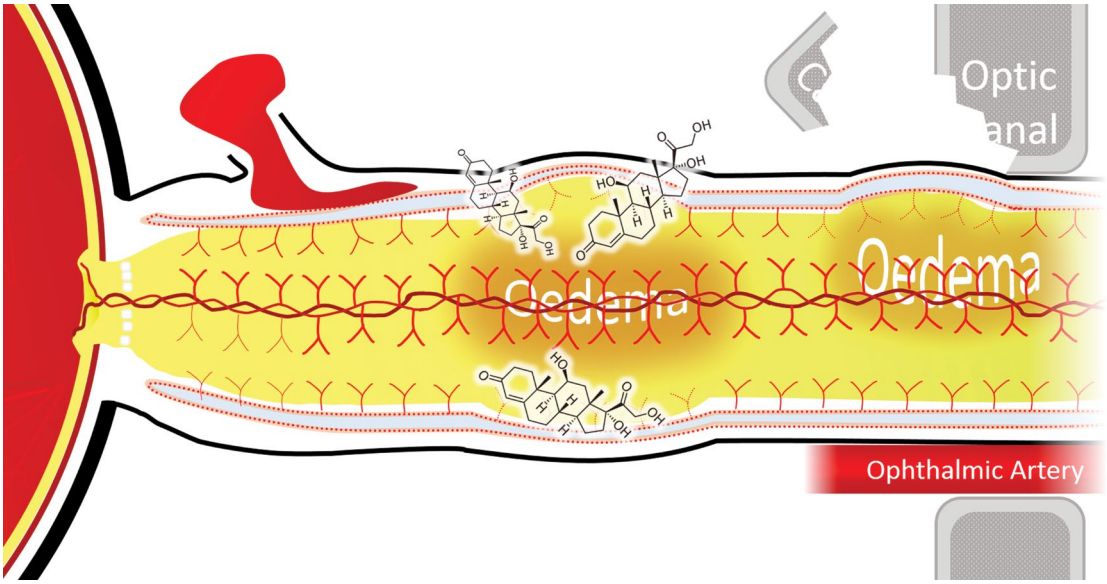


Figure 1. Two-stage model of traumatic optic neuropathy graphically depicting the primary (irreversible) and secondary (potentially reversible) phases.

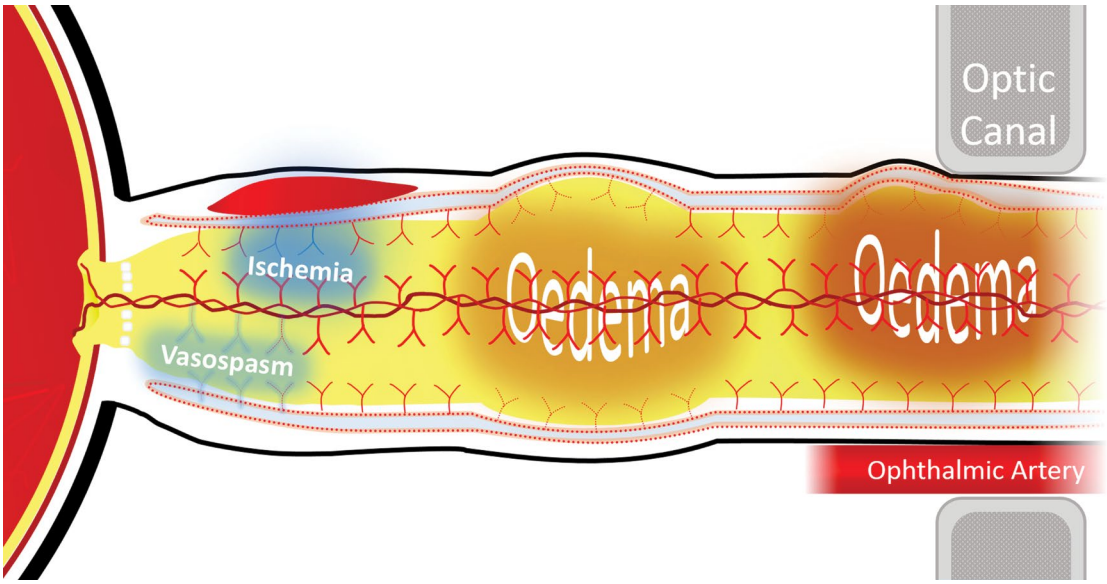


Figure 2. Primary damage to the optic nerve due to avulsion, partial or complete transection may develop as a consequence of impaction of missile or bony fragments.

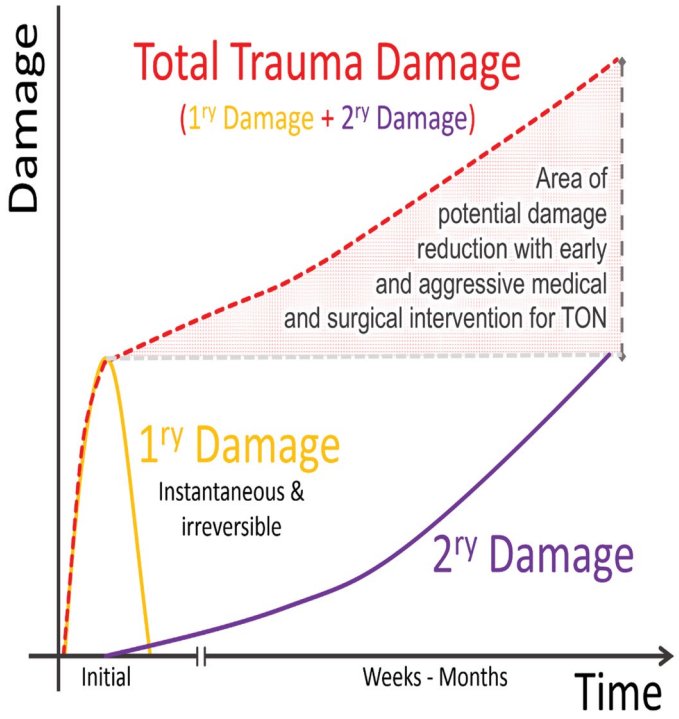


Figure 3. Mechanisms of secondary damage to the optic nerve include ischemia, compression by nerve sheath hemorrhage, and induction of vasospasm leading to edema of the optic nerve within the tight canal. This leads to further compression, worsening of ischemia, inflammatory edema and thus the vicious cycle sets in.

In the direct TON group, the irreversible primary impact is profound and radiologically demonstrable as avulsion, transection or impaction. In indirect TON, the shear stress without disruption of radiological continuity of optic nerve leads to limited primary injury. Here, the potentially reversible secondary damage dominates the pathophysiological process. This observation is also supported by the fact that the vision recovery reported in literature is better in patients with indirect TON as compared to direct TON [19]. Thus the delayed secondary damage forms the basis for early and aggressive medical and surgical intervention for all types of TON. Intervention is aimed at disrupting the vicious cycle with medical or surgical decompression (Figure 4).

Clinical features

There is usually a clear history or evidence of direct trauma to the face, head or eye(s). In some cases, such as those involving children or the elderly, this history can be difficult to elicit. Examination can be limited especially with unconscious patients or patients with altered mental status, which is not uncommon following head injury. The clinician should have a high suspicion for TON in such cases.

TON can be unilateral or bilateral, and the majority of cases are unilateral [2,3,8]. A relative afferent pupillary defect is present except where TON is symmetric and bilateral. Visual acuity (VA) is usually significantly reduced but can be variable, ranging from normal to no perception of light. In an epidemiological study in the UK, presenting VA was 6/60 or worse in 70% of patients and 36% of patients had no perception of light [5]. Impairment of color vision and visual field defects may be present.

External examination may allude to a history of trauma, for example facial or periorbital bruising. The presence of proptosis suggests intraorbital damage to the optic nerve secondary to orbital hematoma or edema.

Certain findings on dilated fundus examination may allude to the location of optic nerve injury. Partial or complete avulsion of the optic nerve head produces a ring of hemorrhage. The optic nerve head may appear as a deep round pit following complete avulsion of the optic nerve head. Venous obstruction and traumatic anterior optic neuropathy may be noted in cases of injury between the globe and where the central retinal vessels enter the optic nerve. Optic disc swelling may be seen in instances where there are hemorrhages in the optic nerve sheath posterior to the origin of the central retinal vessels. Optic disc pallor is only noted 4-6 weeks after the initial injury.

Potential confounders in the diagnosis of TON include other injuries that reduce visual acuity, such as retinal detachment, choroidal rupture, hyphema, and vitreous hemorrhage. Identification of a relative afferent pupillary defect (RAPD) in the affected eye helps to establish a contribution of TON to the vision loss; unless there is extensive damage to the retina, a relative afferent pupillary defect should not be present. Absence of an RAPD effectively excludes TON as the cause of acute unilateral vision loss.

In the acute setting, any potential reversible causes of TON should be excluded. A lateral canthotomy should be performed where there is a retrobulbar hemorrhage. Drainage of air with a retrobulbar needle when there is orbital emphysema may relieve pressure on the optic nerve. Optic nerve sheath hemorrhage may be drained with a sheath fenestration [21].

Investigations

Neuroimaging

While TON is mostly a clinical diagnosis, examination can be challenging in the setting of polytrauma and poor cooperation from patient. Direct TON may be diagnosed based on radiological findings of penetrating foreign bodies, body fragments, expansive lesion (e.g. hematoma, emphysema, edema), or optic nerve canal fracture. The diagnosis of indirect TON can be elusive due to the absence of radiological findings.

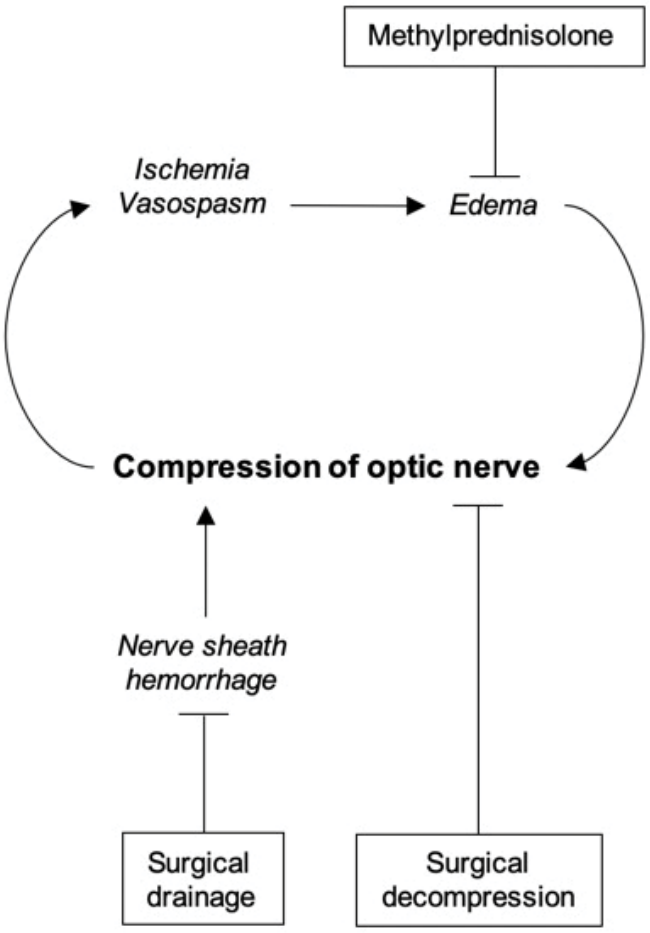


Figure 4. Intervention in TON targets the cascade of compression, ischemia and edema. Medical decompression by methylprednisolone reduces the inflammatory edema. Prompt surgical drainage of sheath hemorrhage and surgical decompression of optic canal relieve the compressive forces mechanically. These interventions disrupt the vicious cycle and thus reduce the ischemia induced secondary damage to the optic nerve.

Computed tomography (CT) and magnetic resonance imaging (MRI) can be used sequentially in the assessment of TON. CT scans are usually the first choice of imaging in the acute setting as it takes a shorter amount of time to complete. CT scans are superior to MRI for characterization of skull vault and facial fractures, and sinuses. Fine cuts of CT scans are also helpful where there is penetrating injury to visualize intraocular and/or intraorbital foreign bodies of unknown material. CT scans can be used to detect any intracranial or orbital hemorrhages. It may also demonstrate an intact optic nerve sheath in the presence of an optic nerve avulsion [18].

Once the presence of a metallic foreign body is excluded, an MRI can be performed to further characterize the injury. MRI is suitable for detecting non-metallic foreign bodies and gives better quality for imaging the orbital soft tissues and visual pathways.

CT helps delineate the relationship of optic nerve and posterior paranasal sinuses. The findings may reveal anatomical variations predisposing the patient to optic nerve injury which influence outcomes. DeLano classified the relationship of the optic nerve to the sphenoid and ethmoid sinuses into four types. In type I, the nerve courses adjacent to sphenoid sinus without impinging the wall. In type II, the nerve in the optic canal indents the sphenoid sinus only. In type III, the nerve runs within the sphenoid sinus and is surrounded by pneumatized sinus. In type IV the nerve courses immediately adjacent to both the sphenoid and posterior ethmoid sinuses. Type II and III optic nerves are predisposed to injury. Another, not uncommon variation is the pneumatized posterior ethmoidal cell, or the Onodi cell, occurring in 8-20% of the population. The optic nerve canal often may be dehiscent within the Onodi cell. Pathology of this cell has been shown to cause visual symptoms as a result of its proximity to nerve. Hemorrhage in Onodi cell may point towards an underlying fracture of the optic canal with an impinging bony fragment injuring the optic nerve.

Various studies have been conducted to evaluate the association of TON with CT findings. Kelishadi SS, et al. described 5 groups of facial fracture patterns associated with TON. Ipsilateral zygomatic bone fractures and ipsilateral maxilla fractures were most and least commonly associated with TON, respectively. In a study of 637 patients, Bodanapally U, et al. found that the CT face findings associated with prediction of TON were intraconal haematoma, intraconal emphysema, optic canal fracture, hematoma along the posterior globe, and extraconal haematoma. Based on these findings, they proposed a scoring system to predict the likelihood of TON. Another study predicted that patients with nasoethmoid complex fractures are approximately 1.6 times more likely to develop TON. This suggests that more central injuries to the face are more likely to result in intraorbital or intracanalicular TON [3].

These findings may aid the diagnosis of TON in cases where clinical signs are less apparent. However, intra-operative findings may have poor correlation with pre-operative neuroimaging results. Hence, it may not be wise to rely completely on pre-operative imaging when using it as a consideration for surgery.

While conventional MRI can detect optic nerve atrophy and optic nerve sheath dilation, it cannot accurately assess early changes preceding the irreversible structural damage.

In a retrospective study of MRI with diffusion weighted imaging (DWI) performed on 29 patients with TON, the mean apparent diffusion coefficient (ADC) in the posterior segment of the injured optic nerve was lower than that in the contralateral uninjured nerve. This reached statistical significance when the scans were performed up to 1 week post-injury.

Diffusion tensor imaging (DTI) is widely recognised as a tool to study central nervous system (CNS) pathologies, such as ischaemic brain injury. Various indices can be derived from DTI to evaluate the integrity of CNS white matter, such as the optic nerve. Fractional anisotropy (FA) is one of the most widely-used parameters. It is a quantitative measure of the summative direction of diffusion of water along axons, reflecting the health of the axon. Radial and axial diffusivities measure diffusion perpendicular and parallel to axon fibres, respectively. Increased diffusivity suggests enlargement of extracellular space, indicating tissue degeneration and reduced structural integrity.

DTI may be employed as a sensitive tool to evaluate TON. However, changes may only be apparent at least 1 week after the initial injury. Bodanapally U, et al. evaluated the directional diffusivities of the optic nerve in patients with unilateral TON using DTI and found that the mean axial diffusivity in the optic nerve segments and the mean diffusivity in the posterior segment on the affected side were significantly lower than that of normal subjects. They also found that the mean axial diffusivity and radial diffusivity were lower in the affected nerve compared to the contralateral nerve of the same patient but these values did not reach statistical significance. The time to imaging ranged 1-15 days with an average of 7 days.

Li H, et al. studied time-dependent changes with DTI, and grouped patients with indirect TON based on time from injury to examination. They found reduced fractional anisotropy (FA) of injured nerves in patients who were examined 7-30 days post-injury, and increased radial diffusivity with decreased axial diffusivity and mean diffusivity in patients who were examined more than 30 days after injury [9].

DTI changes have also been studied in mouse models of optic nerve injury. Xu J, et al. found that death of retinal ganglion cells caused an early and prolonged decrease in diffusion anisotropy. Wallerian degeneration is a process of degeneration of the axon that is distal to the primary injury, and DTI can help to detect this. In one study, mice were subjected to transient retinal ischemia of one eye while the other eye was left as a control. At 3-28 days after ischemia, there was significant reduction in axial diffusivity of the ipsilateral optic nerve and contralateral optic tract, while both the optic nerve and optic tract showed significant increase in radial diffusivity.

Electroretinogram and visual evoked potentials

Electroretinogram (ERG) measures the retina's electrical response to photic stimulation. Specific to TON, the N95 amplitude of the pattern ERG and the amplitude measured from baseline to trough of N95 (BL-N95) has been demonstrated to have a significant correlation with visual acuity. The BL-95 was significantly correlated to ganglion cell-inner plexiform layer.

Visual evoked potentials (VEP) measure the amplitude of occipital lobe responses to visual stimulation. It has value in objectifying visual function in patients who are unconscious, erratic pupillary responses or bilateral TON when presence of RAPD cannot be determined. VEP and ERG can be used in the pre-operative setting to decide if surgery is indicated, and for prognostication. Both tests have the advantage of providing an objective surrogate marker of visual function. While VEP can be used in the unconscious patient, ERG requires patient cooperation to fixate on stimuli. The disadvantages of VEP include that the machine can be bulky, false positive findings are frequent, and results may be inaccurate if visual centers of the brain are damaged.

Ultrasound

In a case study of optic nerve head avulsion, an area of hypolucency at the optic nerve head section was seen on ultrasound. Ultrasound can also be used to visualise any retrobulbar hemorrhage. Doppler examination shows that TON may affect hemodynamics of the central retinal artery.

Spectral-domain optical coherence tomography

Spectral-domain optical coherence tomography (SD-OCT) is a non-invasive tool that provides high-resolution imaging of the retina and helps to diagnose optic nerve disorders.

Lee JY, et al. obtained horizontal and vertical enhanced-depth imaging from SD-OCT scans of the fovea of patients with unilateral TON within 2 weeks of injury. This study found that the choroid at horizontal, vertical and average subfoveal, inner temporal, and outer inferior locations was significantly thicker in eyes affected by TON. The thicker choroid could be due to reduced blood flow and vascular remodeling of the optic nerve head and choroid.

Thinning of macular ganglion cell layer reflects structural damage to retinal ganglion cells and their axons after optic nerve damage. Thus, measurements of retinal nerve fiber layer and macular ganglion cell layer have been used widely in the assessment of diseases of the optic nerve such as glaucoma.

In 2 cases of indirect TON, Lee KF, et al. found thinning of the macular ganglion cell complex that occurred earlier than thinning of the peripapillary retinal nerve fiber layer in a series of sequential wide-field swept source

optical coherence tomography (SS-OCT) over 4 months. This is similar to glaucomatous damage and supports the argument that axonal injury, not retinal ganglion cell injury, is the primary pathology.

In another study of 29 patients with TON, thicknesses of the whole retina, retinal nerve fiber layer and ganglion cell layer plus inner plexiform layer (GC-IPL) at the macula were obtained using SD-OCT. All these measurement areas were 3-36% thinner in TON eyes compared with contralateral uninjured eyes. Furthermore, GC-IPL measurements performed within 3 weeks of injury were significantly thinner than in the uninjured eyes. They also found a positive correlation between the retinal layer thicknesses and visual function (including color vision, visual field, and visual evoked potential).

A longitudinal study of 4 patients with TON evaluated the circumpapillary retinal nerve fiber layer (cpRNFL) and ganglion cell complex using SD-OCT up to 36 weeks post-injury. The cpRNFL thickness and ganglion cell complex decreased significantly at 2 weeks after the injury. Macular thickness, measured using time-domain OCT, started to decrease significantly at 4 weeks after the injury. These measurements may be correlated with visual function, as reported in glaucoma studies, where central visual function and visual field indices were shown to have a significant positive correlation with cpRNFL and GC-IPL thicknesses.

OCT-angiography (OCTa)

OCTa has demonstrated a decreased density of peripapillary capillaries in patients with chronic optic neuropathies. Chen CT, et al. demonstrated localized superonasal peripapillary capillary loss in a patient with TON with a visual acuity of 20/20 and inferior arcuate defect on visual field, three months after trauma. This decreased peripapillary retinal capillary flow density corresponded with the RNFL thinning seen on OCT. They concluded that this decrease in density is secondary to retinal nerve fibre layer loss as a consequence of optic nerve injury.

Management

Currently, the main treatment options available are observation, intravenous (IV) corticosteroids, surgical optic canal decompression, or a combination of corticosteroids and surgery. In primary TON where the pathology can be easily identified, surgical interventions to remove the offending lesion may be more appropriate. For example, in the presence of an optic nerve sheath hematoma, optic nerve sheath fenestration may be performed. Likewise, surgical removal of bony fragments impinging on the optic nerve may be more effective than conservative or medical management. The choice of treatment remains debatable with most cases of indirect TON, when the pathology is less obvious. To date, there is insufficient evidence and guidance in determining the most appropriate treatment. Table 1 summarizes the treatment outcomes for TON in human studies.

Conservative

Outcomes of conservative management have been reported to vary

Table 1. Overview of treatment outcomes for traumatic optic neuropathy in human studies.

Author	Design	Sample Size (number of eyes)	Treatment	Outcome
Ford RL, et al. (2012)	Prospective	26 (26)	Steroids, surgery	No association between treatment and improvement of VA by 3 lines
Pokharel S, et al. (2016)	Non-randomised interventional	10 (10)	Observation, steroids	Steroids beneficial if presenting VA better than NPL
Sefi-Yurdakul N, et al. (2018)	Retrospective	46 (46)	Observation, steroids	Both treatment groups had statistically significant improvement of visual recovery
Yip CC, et al. (2002)	Retrospective	21 (21)	Observation, steroids	No significant difference in improvement of VA by 2 lines between both groups
Sitaula S, et al. (2017)	Retrospective	37 (37)	Observation, steroids	Improvement in vision with steroids, significant with intravenous steroids
Sosin M, et al. (2016)	Retrospective	109 (109)	Observation, steroids, surgery, combination of steroids and surgery	No difference in visual recovery amongst all treatment groups
Lee KF, et al. (2010)	Retrospective	24 (27)	Observation, steroids	Intravenous, followed by oral steroids have better improvement in vision compared to observation alone
Entezari M, et al. (2007)	Randomized double-blind, placebo-controlled	31 (31)	Placebo, steroids	No difference in visual recovery
Levin LA, et al. (1999)	Non-randomized interventional	133 (139)	Observation, steroids, surgery	No difference in visual recovery amongst all treatment groups
Ropposch T, et al. (2013)	Retrospective	42 (42)	Surgery with and without steroids	Lower visual recovery for surgery with steroids
Yu B, et al. (2020)	Randomized interventional	66 (66)	Steroids, combination of surgery followed by steroids	Significantly better visual recovery with immediate surgery and post-operative steroids compared to steroids alone
Li H, et al. (2008)	Non-randomized interventional	237 (237)	Steroids, combination of steroids and surgery	No difference in visual recovery
Kashkouli MB, et al. (2011)	Pilot study	7 (7)	Observation, EPO	Significant visual recovery with EPO
Rashad MA, et al. (2018)	Prospective case series	14 (14)	EPO in recent (< 3 months) and old (3-36 months) TON	Significant visual recovery in recent and old TON
Kashkouli MB, et al. (2018)	Randomized interventional	100 (100)	Observation, steroid, EPO	Significant visual recovery in all groups, not significant when comparing all 3 groups
Acar U, et al. (2017)	Prospective case series	16 (16)	EPO for late ON	No significant visual recovery
Razeghinejad MR, et al. (2010)	Randomized, double-blind, placebo-controlled	32 (32)	Placebo, levodopa. (All patients also received steroids)	Significant visual recovery with levodopa in presenting VA worse than or equal to counting fingers
Fujikado T, et al. (2006)	Prospective case series	8 (8)	TES in TON and NAION	Improvement in VA in 4/5 eyes with TON and 2/3 eyes with NAION
Huang J, et al. (2008)	Case reports	2 (2)	Acupuncture	Improvement of VA in both cases

(VA: Visual Acuity; EPO: Erythropoietin; ON: Optic Neuritis; TES: Transcorneal Electrical Stimulation; TON: Traumatic Optic Neuropathy; NAION: Non-arteritic Ischemic Optic Neuropathy)

widely. 40-60% of cases managed conservatively have improvement in visual outcomes. Majority of TON in the pediatric population were managed conservatively with no significant difference in visual outcomes compared to patients who were treated. Thus, observation alone can be considered acceptable in the management on TON.

Medical

Corticosteroids are thought to facilitate spinal cord impulse generation, enhance spinal cord blood flow, and decrease spinal cord lipid peroxidation and tissue degeneration. The use of corticosteroids in TON stemmed from the findings of the National Acute Spinal Cord Injury Study (NASCIS). After NASCIS 140 in which the dose of methylprednisolone (1000 mg bolus then 1000 mg daily for 10 days) was found to be subtherapeutic, NASCIS 2 was carried out. Patients with acute spinal cord injury were randomized into 3 treatment groups – methylprednisolone, naloxone and placebo. Patients in the methylprednisolone group were given a bolus dose of 30 mg/kg, followed by an infusion of 5.4 mg/kg for 23 hours. They found that patients who received methylprednisolone within 8 hours of injury had significant improvement over those who received naloxone or placebo.

NASCIS 3 aimed to refine the dose and regime of methylprednisolone in patients with acute spinal cord injury. Patients who received methylprednisolone within 3 hours of injury benefited from the 24-hour treatment regime (5.4 mg/kg/hour for 24 hours), whereas patients who received methylprednisolone 3-8 hours after injury benefited from a 48-hour regime (5.4 mg/kg/hour for 48 hours). All patients received a bolus of IV methylprednisolone 30 mg/kg/day.

However, there have been no studies to qualify the suitability and accuracy of extrapolating data from spinal cord injury to TON. Nevertheless, corticosteroids have been widely used and studied in TON.

In a study of 10 cases of indirect TON, 4 patients who received IV methylprednisolone had rapid visual recovery when their initial visual acuity was better than non-perception of light. A retrospective analysis of patients with indirect TON found that IV methylprednisolone was not superior to conservative management. However, this is confounded by the fact that patients who were conservatively managed had significantly better initial visual acuity, which may influence final visual outcomes. Other studies have also reported no significant difference in visual outcomes between methylprednisolone and conservative management [10,11]. In a retrospective review of patients with iatrogenic visual loss as a result of orbital surgery, corticosteroids had no significant effect on visual outcomes.

However, most of these studies are retrospectively reviewed. To date, there has only been one double-masked placebo-controlled randomized clinical trial to evaluate the effects of high-dose methylprednisolone with placebo in patients with TON. Patients in one group received methylprednisolone (250 mg IV every 6 hours for 3 days, then 1 mg/kg orally for 14 days), and patients in the control group received normal saline (50 ml IV every 6 hours for 3 days, then placebo for 14 days). There was no significant difference in final best corrected visual acuity between the 2 groups. The difference between initial and final BCVA in both groups was significant. This suggests that corticosteroids may not help to improve visual outcomes.

As most TON are associated with traumatic head injury, ophthalmologists should confer with neurologists and/ or neurosurgeons prior to commencing methylprednisolone for TON. The Corticosteroid Randomisation After Significant Head Injury (CRASH) is a randomised controlled trial studied the effects of methylprednisolone on death and disability after head injury. The risk of death or severe disability was higher in the corticosteroid group than in the placebo group, suggesting that corticosteroids should not be used routinely in the management of head injury [11].

In animal studies, corticosteroids have been shown to have no effect on retinal ganglion cells survival and axonal regeneration. Steroids may even exacerbate TON as another study found a dose-dependent decrease in axon counts with increasing dose of corticosteroids in mice subjected to optic nerve trauma. Furthermore, corticosteroids are not without side effects. Some side effects include acute pancreatitis, gastrointestinal bleeding, and acute psychosis and wound infections.

Surgical

There are currently no available guidelines for surgical management of TON. The decision for surgical intervention is dependent on the clinician and presenting features of the patient. Review of the current literature have suggested some indications for surgery, which include presenting visual acuity of perception to light or better, failure of, or after corticosteroid treatment, radiological evidence of optic nerve compression, prolonged absolute latency or amplitude reduction with pre-operative VEP41 and optic canal fracture [17]. Documentation of progressive visual decline in the setting of a surgically-treatable cause also can support the decision for surgery.

Contraindications include multiple fractures, multiple bone fragments penetrating the optic nerve, complete optic nerve atrophy, complete disruption of the optic chiasm, presence of a carotid-cavernous fistula, inability of the patient to undergo general anaesthesia, or presence of other significant life-threatening conditions post-injury that require more immediate attention.

In the presence of a retrobulbar hematoma, an urgent transcutaneous trans-septal orbital decompression can be performed to release the pressure of the hematoma on the optic nerve. However, this is contraindicated in the presence of a carotid-cavernous sinus fistula which is suggested by a pulsating exophthalmos.

Expertise of the other surgical disciplines dealing with head surgeries (e.g. otorhinolaryngology, neurosurgery) is required. Due to the rarity of this condition and the wide variation in presenting features, there are no published randomized controlled trials assessing the role of surgery in TON.

Surgical optic nerve canal decompression relieves pressure on the optic nerve by removing dislocated bony fragments. Surgical approaches can be divided into transcranial and extracranial. Extracranial methods include transethmoidal, sublabial, trans-sphenoidal, transnasal and transcaruncular. Recently, the minimally invasive endoscopic transnasal/ transsphenoidal optic canal decompression (ETOCD) has been adopted as the preferred approach due to its better side effect profile and rapid recovery time [15]. Choice of surgical approach will depend on location of the pathology or lesion, and surgeon proficiency. To avoid brain retraction and injury, an endoscopic approach is preferred.

It has been reported that 40.6-63% of patients with TON have improved visual outcomes after ETOCD.42,106,120,125,130 In a recent prospective study of 20 patients with TON, 80% of patients achieved complete recovery of visual acuity. However, the authors did not state the definition of complete or partial recovery, neither were the actual visual acuities made known.

Surgical management in children with TON can be challenging due to the smaller surgical space and difficulty in differentiating the optic canal and internal carotid artery. In children with indirect TON who underwent endoscopic trans-ethmosphenoid optic canal decompression (ETOCD), there was significantly greater improvement of patients with residual vision compared to patients with initial visual acuity of no perception to light.

Aside from the usual complications of surgeries such as infection, complications specific to surgical interventions for TON include cerebrospinal fluid leak, accidental dural exposure, cavernous sinus hemorrhage, and injury to the ophthalmic artery.

Most surgeons advocate early intervention within 2 days to 2 weeks, but some have found no significant difference in outcomes with regards to timing of surgery. A systematic review of ETOCD found that 57% and 58% of patients who received surgery within 3 days of injury and between 4-7 days post-injury had visual improvement. Improvement was seen in 51% of patients who underwent surgery 1 week or more after injury. This suggests that surgical intervention, even if delayed, may be better than none at all. Nonetheless, all of these analyses suffer from potential selection bias and non-uniform inclusion criteria and data reporting strategies.

Reports of navigation-guided surgery have been published. Eighteen of 20 cases of patients with non-traumatic compressive lesions underwent successful resection with no intra- or post-operative complications. Bhattacharjee K, et

al. described 2 cases of TON that underwent navigation-guided optic canal decompression via external transcaruncular approach. Both cases did not have visual improvement after receiving methylprednisolone but had improvement after surgery. Confoundingly, one of these cases had received intravitreal EPO post-surgery.

Combination of corticosteroids and surgical treatment

The International Optic Nerve Trauma Study (IONTS) evaluated outcomes of 133 patients with TON who underwent optic canal decompression surgery, were given corticosteroids, or not given any treatment. There was insufficient evidence to conclude that any treatment should be the standard treatment of choice for patients with TON.

Some studies have found no difference between surgical treatment and corticosteroids. A retrospective study of 42 patients compared the effect of corticosteroids and combined corticosteroid and surgical therapy. 29% of patients treated with combined therapy had improvement in visual outcomes, compared to 53% of patients treated with surgical intervention alone. Addition of corticosteroids had no significant benefit on visual outcomes and in all cases; there was no worsening of visual function. A large prospective non-randomised study of 237 patients reported no statistically significant difference in visual improvement between patients treated with both corticosteroids and ETOCD, and those treated with corticosteroids only.

A recent prospective study evaluated the outcomes between immediate ETOCD treatment and ETOCD with pre-operative steroid treatment. 68 patients with indirect TON were randomised to 2 groups. The first group underwent ETOCD immediately after admission, and received methylprednisolone 20 mg/kg/day for 6 days. The second group received methylprednisolone 20 mg/kg/day for 3 days prior to surgery. There was significantly greater improvement in patients who underwent ETOCD immediately.

Novel therapies

Erythropoietin (EPO), a neuroprotective cytokine with anti-inflammatory, antioxidative and angiogenic effects, can help to prevent apoptosis and promote healing in acute brain injury (e.g. stroke) and chronic neurodegenerative conditions (e.g. multiple sclerosis). In a pilot study of patients with indirect TON, EPO administered intravenously improved final best corrected visual acuity compared to observation alone.

In a recent case series, patients with recent (trauma less than 3 months) and old (trauma between 3-36 months) indirect TON received 1-2 doses of intravitreal 2000 IU erythropoietin. Both groups had significant improvement in their best corrected visual acuity, visual evoked response amplitude and latency.

The Traumatic Optic Neuropathy Treatment Trial (TONTT) compared the effects of observation, IV methylprednisolone and IV erythropoietin. They found that there was significant improvement in best corrected visual acuity in all groups of patients, and significant improvement in colour vision in the EPO group, with no recorded side effects.

Acar U, et al. evaluated the effects of delayed administration of intravitreal EPO on patients with late-stage optic neuropathy. 25% (4 in 16) of these patients had TON, and the mean time interval between the first symptom of optic neuropathy and the first injection was 11.63 months (range 7-20 months). All these patients had also received IV corticosteroid therapy at the time of diagnosis. A total of 3 intravitreal EPO injections were given at 6-week intervals at a dose of 2000 IU/ 0.2 ml. There was no statistically significant difference between the initial and final visual function (as determined by best corrected visual acuity, average RNFL thickness, ERG, VEP and IOP measurements).

The neurotransmitter dopamine and its effects on the central nervous system is well-documented in the pathophysiology of Parkinson's Disease. The retinal amacrine and interplexiform cells are dopaminergic neurons. Dopamine is released during depolarisation or in response to stimuli e.g. light. It acts via dopamine receptors and has effects on retinomotor movements, photoreceptor light responses, electrical coupling between rods and cones, and on supporting horizontal and bipolar cells.

The peripheral conversion of its precursor levodopa can be inhibited by carbidopa. This allows greater concentrations of levodopa to cross the blood-brain barrier and be converted to dopamine. A randomised double-blind placebo-controlled study found that patients who were prescribed levodopa-c tablets (levodopa 100 mg/ carbidopa 10 mg) at a dose of 1 tablet 3 times a day for 1 month had significant improvement in visual acuity after correcting for baseline visual acuity. Treatment was administered within 6 days of injury and all patients received methylprednisolone therapy (250 mg IV every 6 hours for 3 days than 1 mg/kg orally for 11 days then tapered over 3 days). There were no reported side effects and no patient experienced worsened visual acuity. This suggests that combined levodopa/ carbidopa and methylprednisolone treatment can be considered in TON.

Tumor necrosis factor (TNF) is a pro-inflammatory cytokine associated with neurodegenerative conditions. TNF production has been shown to be increased following optic nerve injury. A recent study found that TNF-alpha pre-injected in mice models attenuated retinal ganglion cell loss and ganglion cell loss was more severe in Tnfα–/– mice. In the long-term, a single exposure to TNF-alpha induced extrinsic apoptosis in retinal ganglion cells. This suggests that TNF-alpha may have a protective role in early optic nerve injury.

Another study utilized immunohistochemistry and quantitative real-time polymerase chain reaction and confirmed upregulation of TNF protein and gene expression within 24 hours of injury, as confirmed by Tse BC, et al. [4]. They also injected etanercept, a TNF inhibitor, into mice immediately after optic nerve trauma. Mice which received etanercept had higher retinal ganglion cell survival and significantly higher a-wave amplitudes on pattern electroretinograms than untreated injured controls, suggesting that suppressing TNF in optic nerve injury may improve visual outcomes.

Pigment epithelium-derived factor (PEDF), secreted by Müller cells and astrocytes, has neuroprotective, anti-angiogenic, anti-inflammatory, anti-oxidative and anti-tumorigenic properties. Intravitreal injection of PEDF in mice models of optic nerve injury has been shown to promote greater survival of retinal ganglion cells.

Adenosine, acting via A2A receptors, has anti-inflammatory effects and is protective against retinal injury in TON. Adenosine is broken down by adenosine kinase. Ahmad S, et al. demonstrated significant reduction in inflammatory cytokines in mice who were treated with an adenosine kinase inhibitor.

Most of the research for these biological agents has been performed only on animals. More research needs to be carried out to determine the best route for administration, dose, side effect profile and efficacy in humans.

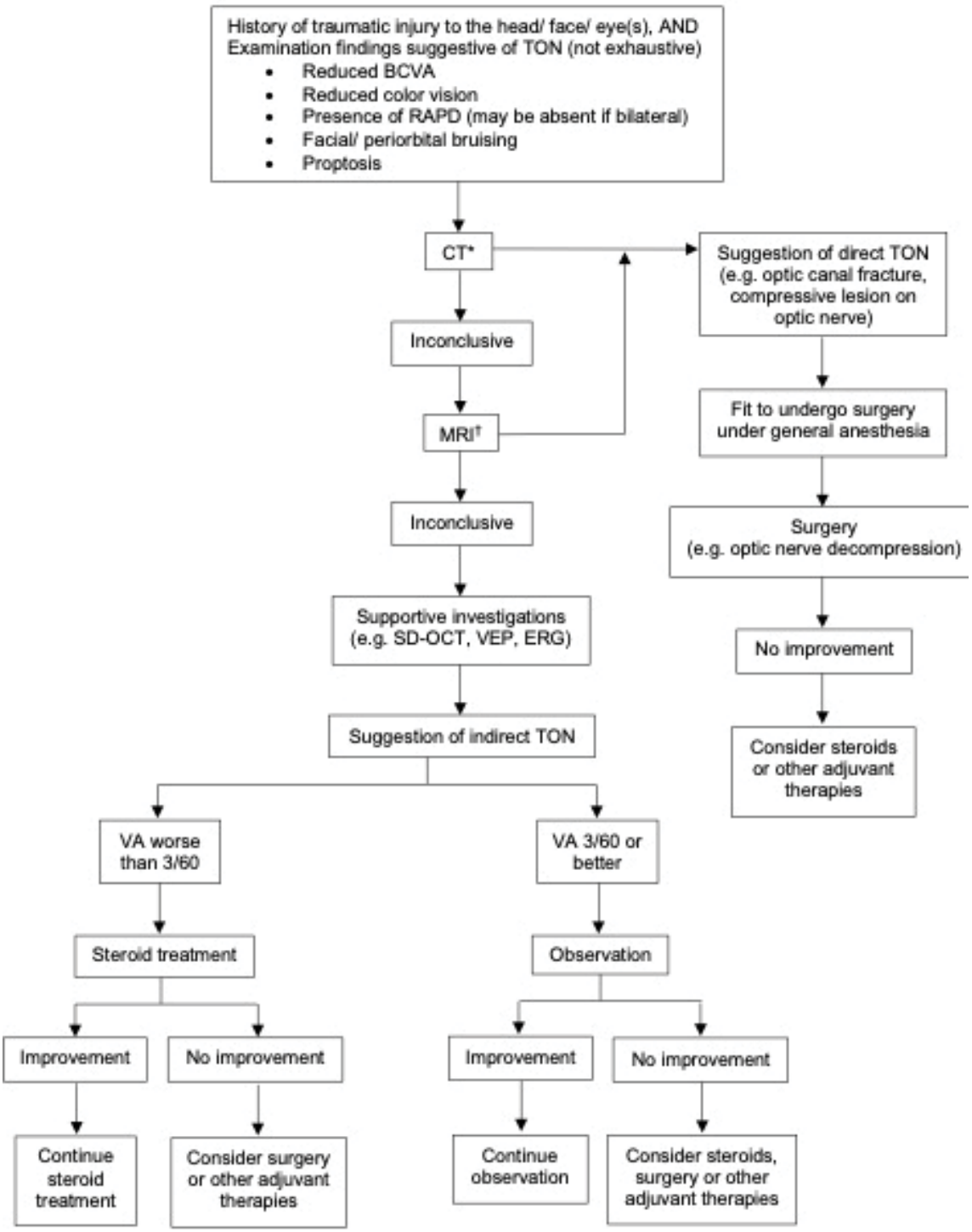
Transcorneal electrical stimulation (TES) is a non-invasive method that increases the chorioretinal blood flow, although the exact mechanism is still undetermined. It may be neuroprotective via the upregulation of neurotrophic factors produced by Müller cells. Using a contact-lens type stimulating electrode, TES has been found to improve visual function in 5 TON patients. None of the patients' visual acuity worsened and 1 patient experienced a mild superficial punctate keratopathy which healed the following day. TES is in its early stages of research but it may be effective in TON with minimal effects on intraocular pressure and systemic effects.

There are 2 case reports of successful treatment of TON with Chinese acupuncture. It has little side effects and is relative non-invasive. However, the exact mechanism is not known and the possibility of response bias cannot be excluded.

Prognosis

Approximately 50% of all patients are left with 'light perception' or 'no light perception' vision, making TON a significant cause of permanent vision loss.

Indicators of poor visual prognosis despite intervention include orbital fracture, significant head injury, hemorrhage in ethmoid and/ or sphenoid sinus, poor initial visual acuity, loss of consciousness, increased age and lack of improvement following 48 hours of treatment. Hemorrhage in the ethmoid or sphenoid sinuses cells possibly indicates a greater amount of energy applied to this region hence, this is associated with a worse visual prognosis.



*A non-contrast Computed Tomography (CT) of the orbit and paranasal sinuses with both bone and soft tissue windows should be performed. Volumetric helical CT acquisition for reconstruction should be employed for designating the bony and soft tissue injury pattern.

†Magnetic Resonance Imaging (MRI) should be performed in patients only after an initial CT scan has ruled out metallic foreign bodies. The standard protocol should include T2 fat suppressed, diffusion weighted imaging and T1 axial and coronal sections of the orbit and paranasal sinuses.

Figure 5. Step by step guidelines for clinical approach, investigations and intervention in a patient with traumatic optic neuropathy.

The impact of presence of optic canal fracture on visual outcomes in patients who underwent ETOCD is varied with some studies demonstrating a negative correlation, others did not find any effect, and one study noted better visual outcomes post-surgery.

Guy WM, et al. performed a retrospective study in 12 patients with a second TON in which time between the 2 TON events was 2-15 years. While all patients had significant vision improvement after the initial injury, their vision dropped to or below their vision after the first injury despite intervention. This raises the possibility that there is a certain amount of optic nerve reserve that was lost during the first injury, making patients more susceptible to permanent vision loss after the second injury.

Conclusion

TON is largely a clinical diagnosis that can be supported by various investigations. A single investigation may not be sufficient in the diagnosis of TON as the results can be varied. Selective findings from multiple investigations should be combined and may shed more light on the diagnosis of TON where the diagnosis is not so apparent.

More quality studies are needed to evaluate the outcomes of various treatments and the effects of combinations of therapies. Management of the patient with TON must be individualised based on the clinical picture or presence of associated injuries. Clinicians and patients may choose a more conservative/ medical approach in the first instance and opt for surgery if medical treatment fails. They may also wish to opt for surgery as first-line intervention in cases when the presenting visual acuity is perception to light or worse. We propose a guideline of treatment options that the clinician may use when faced with a patient presenting with TON (Figure 5). More studies will be needed to evaluate the effective cut-off for VA when deciding between steroid treatment or observation, and to determine the best steroid dose and regimen.

While care is focused on the affected eye in unilateral cases, it is also important to examine and monitor the fellow eye. A case report found VEP and functional MRI changes in the contralateral eye. This suggests that trauma to one eye activates bilateral glial processes in the retinal ganglion cells and the rest of the visual pathway in humans, as previously demonstrated in animal models.

Declarations

Methods of literature search

A literature search was conducted using the following search engines: PubMed, MyAthens, ScienceDirect, Google, and personal knowledge of the subject.

Disclosures

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Conflicts of interest

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Highlights

- Craniofacial trauma may lead to optic nerve injury and profound vision loss
- Standard of care is not yet established; treatment has to be individualized
- Imaging helps identify anatomical risk factors including predisposed optic canals
- Direct type of injury usually requires surgical decompression
- In the indirect type, a trial of steroid therapy may be offered initially

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