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Review

Updating traumatic optic neuropathy

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Traumatic optic neuropathy (TON) is the affectation of the visual function, secondary to a damage caused by a direct or indirect traumatic mechanism over the optic nerve. It occurs in approximately 0.5 to 5% of closed head injuries, and in 2.5% of patients with maxillofacial trauma and mid-face fractures. The types of TON are direct, anterior indirect, posterior indirect, and chiasmal. This work aims to offer an updating in traumatic optic neuropathy. We made a search in international data bases such as PubMed, ClinicalTrial, Ebsco, Hinari and so on, and found 32 articles which were used in this review article. We used the following keywords: traumatic optic neuropathy, optic nerve, trauma, visual loss, visual disease. 70% of the articles correspond to the last five years. This review was redacted using Microsoft Office Word 2016 in a laptop Asus with Window 10 system. We made a compilation with diverse therapeutic options based principally in axonal regeneration developed by researchers during the last decade. The present review article provides an updating regarding potential strategies for axonal regeneration and optic nerve repair, focusing on the researches of many investigators around the world. Nowadays, therapeutic options have advanced in many fields, but still more researches must be done to find a definitive solution for traumatic optic neuropathy in a near future.

Key words: Traumatic optic neuropathy, optic nerve, trauma, visual loss, visual disease.

INTRODUCTION

The visual diseases are a real health problem with high repercussion for individuals, the family and society. In the world there are approximately 285 million of people with visual disability; 39 million are blind and 246 million have low vision (WHO, 2014).

Visual loss could be caused by different etiology. Worldwide, non-corrected refractive defects are the most important cause of visual disability, but in countries with low and medium earned income, cataracts are still the principal cause of blindness (WHO, 2014). In no few times, visual loss could be due to the optic nerve damage or optic neuropathy (Fuentes et al., 2014), such as: ischemic, demyelinating, hereditary, tumoral, toxic-nutritional, inflammatory, glaucoma, and traumatic. This research concentrates on traumatic optic neuropathy (TON). This entity is defined by the American Academy of Ophthalmology as the partial or totally affectation of the visual function, secondary to a damage caused by a direct or indirect traumatic mechanism over the optic nerve (American Academy of Ophthalmology, 2014-2015). Since more than a half of century, some authors (Mariotti, 1952; Hsu, 1952; Lazorthes and Anduze, 1952) from different parts of the world have been talking about this entity, and nowadays it is continuous being a concern for the researchers. For that reason, we have the objective to offer an updating in traumatic optic neuropathy.

Every year, 500 000 patients are notified with unilateral

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traumatic blindness (Fuentes et al., 2016). Traumatic optic neuropathy occurs in approximately 0.5 to 5% of closed head injuries, and in 2.5% of patients with maxillofacial trauma and midface fractures (Chan, 2007). A recent study (Singman et al., 2016) asserts that in populations in England, for both adults and children, the overall incidence of traumatic optic neuropathy is approximately 1/million; notably, approximately 80% of the patients were males, and the majority of cases suffered relatively minor head injuries with neither orbital nor skull fracture. This suggests that indirect traumatic optic neuropathy may be more common than direct traumatic optic neuropathy.

MATERIALS AND METHODS

A search in international data bases such as PubMed, ClinicalTrial, Ebsco, Hinari, Scielo, Cochrane and found 32 articles in Spanish and English languages principally, which were used in this review article were made. The following keywords were used: traumatic optic neuropathy, optic nerve, trauma, visual loss, visual disease. The 70% of the articles corresponds to the last five years, showing a high actualization level. This review was redacted using Microsoft Office Word 2016 in a laptop Asus with Window 10 system.

RESULTS AND DISCUSSION

After searching and reading many articles, the following classification of different types of traumatic optic neuropathy still valid today was found.

Types of traumatic optic neuropathy (Lessell, 1991)

Direct

Penetrating object causing direct injury to the optic nerve by complete or partial transaction of nerve or contusion of nerve; hemorrhage or foreign body compressing the optic nerve; initial variable level of vision that often worsens. Orbital hemorrhage may cause orbital compartment syndrome. Enlarged optic nerve sheath may be seen on CT scan.

Anterior indirect

Sudden rotation of anterior displacement of globe with object causing injury to the anterior segment of the optic nerve, often at the cribrosa sheet. Rare type of traumatic optic neuropathy. Peripapillary vitreous hemorrhage. Partial or complete optic nerve head avulsion. Papilledema, venous congestion, central retinal artery occlusion, retinal edema.

Posterior indirect

Frontal or midfacial trauma or trauma that may appear trivial causing indirect optic nerve injury; most common type of traumatic optic neuropathy. No ophthalmoscopic signs of injury. Afferent pupillary defect and/or dyschromatopsia. Immediate visual loss is common. Delayed or progressive visual loss occurs in a few cases. Loss of consciousness and midfacial fractures are common. Variable visual field defects. Optic canal fracture on CT does not correlate with severity of optic neuropathy.

Chiasmal

Severe closed head injuries or an abrupt traction on the globe may cause chiasmal injury; variable visual field defects. Central visual acuity may be normal. Anosmia, diabetes insipidus, or other endocrinopathies; skull base fractures and other neurological deficits may be present.

Production mechanism

About production mechanism we can say that two basic mechanisms for TON are understood. Saxena et al. (2014) explain: Direct mechanical injury to the optic nerve causes a tear or interruption of the nerve which has a worse prognosis. Indirect injury is a closed injury causing a reactionary edema in the nerve sheath which can compromises the vascular supply and neurotrophic supply of the ganglion cells by compressing the nerve in the tightly packed optic canal. In both processes, there is retrograde degeneration of the ganglion cells which are irreversibly lost.

Based on 174 postmortem examinations by Crompton (Crompton, 1970) on patients who died after closed head trauma, optic nerve dural sheath hemorrhages was found in 83% of patients. Interstitial optic nerve hemorrhages occurred in 36% of these patients; two-thirds had the hemorrhage within the optic canal; tears and ischemic lesions occurred in 44% of patients; in 81%, these involved the intracanalicular optic nerve, and in 54% these affected the intracranial optic nerves (Crompton, 1970).

The nerve and its sheath are tightly fixed to the bony canal within a confined space. In indirect TON cases, optic nerve injury results from shearing forces to the fibers or to the vessels supplying the nerve. Cadaveric skull studies (Saxena et al., 2014) have demonstrated that if a force is given at the frontal bone or malar eminences they are concentrated and transferred to the optic canal. As the dural sheath is tightly adhered to the periosteum inside the optic canal this force is transferred to the nerve. Such injury leads to ischemic injury to the optic nerve axons within the optic canal followed by optic nerve swelling. This increases the intraluminal pressure of the canal further exacerbating axonal degeneration and compromises the vascular blood supply (Saxena et al., 2014). Less frequently is bilateral traumatic optic

neuropathy, but there is a case reported by Allon et al (Allon et al., 2014) where they explain: There was no contact between the hematomas and the nerve, and there was no direct compression on the nerve. The injury was facial, similar to previous reports of TON.

Other authors also say that the primary TON is involved in overactive, rupture, contusion, and distort of the optic nerve. This type of injury always leads to immediate blindness. The secondary TON may be compromised by nerve edema both within the confines of the bony optic canal and the optic sheath (He et al., 2015). Apoptosis is programmed cell death involving active cellular processes through final common pathways. Injured retinal ganglion cells release extracellular glutamate that induces excitotoxicity (Vorwerk et al., 2004). High glutamate concentrations activate N-methyl-d-aspartate (NMDA) receptors that allow entry of excessive calcium into the cell. It has been shown that optic nerve crush leads to an increase in extracellular vitreal glutamate, but the steps by which axotomy induces excitotoxic damage to ganglion cells is still being studied (Chan, 2007).

Besides ischemia, inflammation contributes to further neural damage. Mediators of inflammation are released to attract polymorphonuclear lymphocytes and macrophages (Chan, 2007). Within the first 2 days after injury, polymorphonuclear lymphocytes predominate to cause immediate tissue damage. They are then replaced by macrophages by about 7 days after injury. These macrophages are thought to contribute to delayed tissue damage, as in delayed posttraumatic demyelination (Kanellopoulos et al., 2000). Macrophages release glial promoting factors. This astroglial response after spinal cord injury may inhibit axonal regeneration processes. Inhibition of macrophage responses have been shown to decrease reactive gliosis, as shown in spinal cord injury studies (Schuettauf et al., 2000).

Diagnosis

The diagnosis can be clinically confirmed paying attention to signs and symptoms referred by patients. They can refer reduced visual acuity, color vision, and/or visual field, as well as a relatively afferent pupillary defect. Direct ophthalmoscopy of the nerve is also expected to appear normal, though optic atrophy or pallor is expected to develop. Automated visual field testing should be offered; however, the vision of subjects may be too poor to glean useful results. In most cases, testing with visual evoked potentials (VEP) is not needed to establish the diagnosis. However, in questionable cases, VEP may provide confirmatory data. VEP may also have predictive value; patients with better responses on VEP may be more likely to regain some or all of their vision (Singman et al., 2016).

With all these signs and symptoms, traumatic optic neuropathy can be usually confused with other entities that cause damage to the optic nerve. For that reason, it is necessary to know the differential diagnosis with other diseases. Ischemic optic neuropathy refers to infarction of any portion of the optic nerve from the chiasm to optic nerve head. Clinically, it is divided into anterior and posterior forms by the presence or absence of swelling of the optic nerve head, respectively; findings in unilateral ischemic optic neuropathy include a relative afferent pupillary defect and demonstrable visual field loss (Patel and Margo, 2017).

Optic neuritis has great variety of visual field defects, contrast sensibility alterations, and edema of the disc (Kanski, 2016). Therefore, the relatively afferent pupillary defect can be very important to establish the difference with other optic neuropathies; speed, constriction radius and latent are more decreased in optic neuritis than in ischemic optic neuropathy (Yoo et al., 2017). In posterior optic neuritis the direct ophthalmoscopy of the nerve is normal, like in initial TON. Other disease with optic nerve damage is Cuban epidemic optic neuropathy, but this has a typical standard fundoscopy with bilateral loss of the retinal nerve fiber layer with the shape of bow tie in the disc-macular bundle; and sectorial temporal disc pallor (Fuentes, 2011). This entity appears as an epidemic (Fuentes, 2016) and it is not the case of traumatic optic neuropathy which has the precedent of trauma and visual recovery in patients with severe trauma, especially in those in whom visual acuity could not be obtained due to various factors, because the initial visual acuity is the strongest predictor of visual recovery (Bodanapally et al., 2015).

Lee et al. (2016) found significant thinning of the entire retina, retinal nerve fiber layer, and ganglion cell layer plus inner plexiform layer (GCIPL) in TON eyes, and a remarkable reduction of GCIPL in early phase TON. They also demonstrated a correlation between morphological changes in the retinal layers and visual functions, including visual field defect and P100 latency and amplitude. Therefore, analyzing each retinal layer using SD-OCT was helpful to understand TON pathophysiology and assess optic nerve function.

About treatment

The basic concept is to decompress the nerve by either decreasing the edema by steroid therapy or creating more space by surgical decompression. But nowadays, therapeutic options are on the way of axonal regeneration. Saxena et al. (2014) assert the controversy in therapy of TON primarily stems from two facts. Firstly, literature lacks a well−executed randomized controlled clinical trial, due to both the relative difficulty in recruitment of adequate numbers and the highly heterogeneous presentation of such patients. The second reason is the unpredictable yet frequent incidence of spontaneous recovery.

Corticosteroids have also been offered to patients for TON. A Cochrane review from 2013 (Yu-Wai-Man and Griffiths, 2013) found one double masked, placebo-controlled and randomized study in which high-dose IV corticosteroids were offered within 1 week of the injury causing ITON; there was no significant benefit over observation.

But, treatment of TON with steroids is strictly contraindicated in cases where severe head trauma accompanies the ocular damage. In cases without head trauma steroid treatment may be applied, although its benefit is questionable (Allon et al., 2014). The International Optic Nerve Trauma Study (Levin et al., 1999) similarly concluded that neither steroid therapy nor decompression showed clear benefits.

According to He et al. (2016), in China, currently surgical decompression of the optic canal is the main approach for traumatic optic neuropathy in neurosurgery. Theoretically, optic nerve decompression reduces intracanalicular pressure and allows the removal of any impinging bony fragment, assisting in the reestablishment of nerve function. They apply different surgical techniques (endoscopic, transorbital and transcranial approaches). They also say that it is generally believed that endoscopic optic nerve decompression offers several advantages over other surgical approaches. It requires no external incision. There is no orbital retraction during the procedure. The endoscopes could provide an optimal visual field.

A pilot study exploring the efficacy of intravenous erythropoietin has been published (Entezari et al., 2014). The drug was administered within 2 to 3 weeks of onset, and the treated cohort demonstrated improved best corrected visual acuity. Notably, the rationale for this treatment was that erythropoietin may provide neuro-protection and support axonal growth.

We also found a study (Morgan-Warren, 2013) that concluded: Laboratory studies are unlocking multiple extrinsic and intrinsic factors, and the candidate signaling pathways responsible for retinal ganglion cell (RGC) death and axon regeneration failure in the adult visual system that could be targeted for clinical treatment. The phosphoinositide-3-kinase and serine/threonine kinase (PI3K/Akt) pathway, which mediates axon growth and protein synthesis through glycogen synthase kinase (GSK3b) and mammalian target of rapamycin (mTOR) signaling, respectively, is a promising candidate pathway, altering the balance of signaling in mTOR and linked pathways to promote RGC survival and axon regeneration.

The use of mesenchymal stem cells in cell therapy in regenerative medicine has great potential, particularly in the treatment of nerve injury. Umbilical cord blood reportedly contains stem cells, which have been widely used as a hematopoietic source and may have therapeutic potential for neurological impairment (Chung et al., 2016).). We also found another article (Jiang et al., 2013) that certifies the use of umbilical cord blood stem cells for traumatic optic neuropathy; but, by the moment, the experimentation is just in animals.

We knew about the first confirmatory, large-sample, double blind, randomized, multi-center clinical trial to establish the efficacy and safety of repetitive transorbital alternating current stimulation (rtACS) in patients with vision impairments caused by optic nerve damage (Gall et al., 2016). This trial is a new and important advance in the search of the best treatment for TON.

Researchers continuously talk about axon regeneration and we found another article (Li et al., 2017) published last year that provides an overview regarding potential strategies for axonal regeneration of RGCs and optic nerve repair; it focuses on the role of cytokines and their downstream signaling pathways involved in intrinsic growth program and the inhibitory environment together with axon guidance cues for correct axon guidance. A more complete understanding of the factors limiting axonal regeneration will provide a rational basis, which contributes to develop improved treatments for optic nerve regeneration.

Still other treatments are in varying stages of development such as acupuncture (Huang and Qian, 2008), drugs (Chien et al., 2015; Bei, 2017), brimonidine (Lindsey et al., 2015), and another therapeutic options (Henrich-Noack, 2013; Kyung et al., 2015; Dun and Parkinson, 2017). The mechanism of the protective effect needs further in-depth study; however, all these findings are encouraging and open the possibility that further treatment and researches may become achievable in the future.

Conclusion

Traumatic optic neuropathy is an affectation that can cause visual loss; so, we consider it important to do this review article trying to make an updating in the most important aspects of TON. The present review provides an updating regarding potential strategies for axonal regeneration and optic nerve repair, focusing on the researches of many investigators around the world. Nowadays, therapeutic options have advanced in many fields, but more researches must be done to find a definitive solution for traumatic optic neuropathy in a near future.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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