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CLINICAL REVIEW

Diseases of the retina and the optic nerve associated with obstructive sleep apnea

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SUMMARY

Many associations between ocular disorders and obstructive sleep apnea (OSA) have been studied, such as nonarteritic anterior ischemic optic neuropathy, glaucoma, papilledema, retinal vein occlusion, eyelid hyperlaxity, lower-eyelid ectropion and recurrent corneal erosions. The objective of this review is to synthetize the possible vascular disorders of the retina and the optic nerve associated with sleep apnea patients and to discuss the underlying pathophysiological hypotheses. Main mechanisms involved in the ocular complications of OSA are related to intermittent hypoxia, sympathetic system activation, oxidant stress, and deleterious effects of endothelin 1. The main evidence-based medicine data suggest that OSA should be screened in patients with ischemic optic neuropathy and diabetic retinopathy. The effect of OSA treatment and emerging therapies are discussed.

Introduction

Ocular diseases potentially associated with obstructive sleep apnea (OSA) include nonarteritic anterior ischemic optic neuropathy (NAION), glaucoma, papilledema, and retinal vein occlusion (RVO), eyelid hyperlaxity, lower-eyelid ectropion, blepharochalasis, keratoconus, xerophthalmia, and recurrent erosions of the corneal epithelium [1]. The pathophysiological mechanism related to OSA that causes these disorders, notably in the retina and optic nerve, are uncompletely known. By contrast, many recent prospective studies reported the incidence and prevalence of ocular diseases in OSA patients. Due to the frequency of OSA in the elderly population, there is a need to understand and evaluate the impact of OSA on the eye physiology. This could help the non-ophthalmologist clinician to know which ocular screening should be performed in OSA patients and guide the ophthalmologist when screening of OSA is important.

The objective of this review is to describe vascular disorders of the retina and the optic nerve in sleep apnea patients and to discuss the underlying pathophysiological mechanisms.

Methods

We conducted a systematic literature search of the NIH database (https://www.ncbi.nlm.nih.gov/pubmed) for all papers published before May 2016, using the following search terms: “obstructive sleep apnea”, “retina”, “optic nerve”, “glaucoma”, “primary open angle glaucoma”, “non-arteritic/nonarteritic anterior ischemic optic neuropathy”, “retinal nerve fiber layer”, “papilledema”, “diabetic retinopathy”, “retinal vein occlusions”, “central serous chorioretinopathy”, “retinal arteries”, “retinal vasculature”, “retinal diameter”, “ocular blood flow”, and “intraocular pressure”. Articles

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Abbreviations

AHI	apnea hypopnea index
AHT	arterial hypertension
BF	blood flow
BP	blood pressure
CRA	central retinal artery
CSCR	central serous chorioretinopathy
CI	confidence interval
CPAP	continuous positive airway pressure
DR	diabetic retinopathy
ET-1	endothelin 1
HIF1	hypoxia inducible factor 1
HR	hazard ratio
ICH	intracranial hypertension
ICP	intracranial pressure
IH	intermittent hypoxia
IL	interleukin
IOP	intraocular pressure
NO	nitric oxide
NAION	nonarteritic anterior ischemic optic neuropathy
NTG	normal tension glaucoma
OA	ophthalmic artery
ONH	optic nerve head
OPP	ocular perfusion pressure
OR	odds ratio
OSA	obstructive sleep apnea
PCAs	posterior ciliary arteries
PDR	proliferative diabetic retinopathy
POAG	primary open-angle glaucoma
RDI	respiratory disturbance index
RNFL	retinal nerve fiber layer
RVO	retinal vein occlusion
T2D	type 2 diabetes
VEGF	vascular endothelial growth factor

Glossary of terms

Retinal nerve fiber layer: this layer is composed of retinal ganglion cell axons and represents the innermost layer of the retina (adjacent to the internal limiting membrane and vitreous body). These axons, after crossing the sclera through the lamina cribrosa, give rise to the optic nerve

Optic nerve cupping: the term “cup” refers to the central portion of the optic disk. During glaucoma progression, death of retinal ganglion cells lead to the loss of axons and then to an enlargement of the optic nerve cupping

Papilledema: optic disc swelling

published before May 2016, in English or French, were considered for review.

The results were first reviewed by analyzing the abstract, and case-reports, reviews, duplicates and irrelevant topics were excluded from further analysis (Fig. 1).

All remaining studies related to the subject were downloaded in full-text format for detailed analysis. Studies were included in this review if they met the following criteria: 1) the population of interest consists of OSA patients, 2) the endpoint is the prevalence of OSA in the corresponding population with the targeted retinal/optic nerve affection, or the prevalence of these affections in an OSA population, or 3) a report of the relation between OSA and/or continuous positive airway pressure (CPAP) and ocular parameters: intraocular pressure (IOP) and retinal nerve fiber layer (RNFL) thickness.

We extracted data using a data-collection form relevant for each retinal/optic nerve disease studied. The main information recorded was: names of the authors, publication year, study type, number of patients in each group, inclusion and exclusion criteria, general methodology for retinal/optic nerve and OSA evaluation, OSA and retinal/optic nerve diagnosis criteria, method used for RNFL measurement, statistical methodology and statistical results (prevalence, odds or risk ratio).

Pathophysiological hypotheses relating OSA to retinal and optic nerve disorders

The deleterious mechanisms activated during the nocturnal sequences of apneas/hypopneas are well described [2], and contribute to the increased risk of cardiovascular events in OSA patients. These mechanisms, among which sympathoactivation, oxydative species and pro-inflammatory mediators release and their consequences in vascular endothelial function, represent potentially harmful effects for the optic nerve and retina.

The blood flow (BF) self-regulation mechanisms, most particularly in the retina and optic nerve head (ONH), pursue the objective of maintaining constant delivery of oxygen, despite variations in ocular perfusion pressure (OPP) or blood saturation in oxygen. Several factors associated with OSA may alter ocular BF regulation:

1) Hypoxia: leads to a vasodilation ranging from +5 to +9% in the retinal capillaries [3] and a +15 to +38% increase in ONH BF [4,5] permitting to maintain tissue oxygenation.
2) BP and OPP variations: OPP depends on systemic BP and IOP, according to the formula OPP = BP − IOP. Retinal BF remains constant for up to 40% increase in BP in human [6], whereas ONH blood flow is ensured up to a 34% increase in OPP [7]. Moreover, an increase in IOP up to 30–45 mmHg, leading to OPP decrease, is also associated with regulation of ONH and retinal BF [8]. Thus, AHT associated with OSA and BP variations during apneas activate chronically and acutely the OPP self-regulation mechanisms, and could have deleterious effects for retinal and ONH vasculature.
3) Alteration in the vasoconstrictive/vasodilatory balance: the main vasoactive agents altered during OSA, ET-1 and NO, are involved in ocular BF self-regulation mechanisms [9] and are potentially associated with ocular vascular self-regulation modifications, in particular during apneas. Additionally, ET-1 plays a role in the proliferation of ONH astrocytes and the death of retinal ganglion cells and the disruption of axonal transport within the optic nerve [10]. Thus, activation of the hypoxia–tumor necrosis factor α–ET-1 axis could play a major role by this way in the pathophysiology of optical neuropathies in OSA patients.

The main pathophysiological mechanisms associated with OSA and their potential effect at the ocular level are summarized in Fig. 2.

Nonarteritic anterior ischemic optic neuropathy

Nonarteritic anterior ischemic optic neuropathy is an ischemic disorder of the anterior portion of the optic nerve, clinically