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Research article

Optic neuropathy related to Onodi cell mucocele: a systematic review and meta-analysis of randomized controlled trials

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Abstract: Background: Onodi cells (OC) are important for rhinologists because they contain the optic canal, and are close to the optic nerve and internal carotid artery. Therefore, any pathologic processes within OCs, including infectious or inflammatory sinusitis, fungus ball, inverted papilloma, mucocele, or sino-nasal malignancy can cause devastating ophthalmologic complications. We aimed to define the different optic neuropathy conditions related to isolated OC mucoceles, determine the different symptoms of each condition and its risk factors, and explore the efficacy of the relevant diagnostic tools and treatment strategies. **Methodology:** A comprehensive electronic search with time and language restrictions was conducted. Several known databases were included: PubMed, The Cochrane Library, and Web of Science from 1990 to 2020. We combined the search terms and limited the study to the English language. We removed duplicates, and the articles were screened based on title, abstract, and full text according to the PRISMA checklist. **Results:** The electronic search strategy conducted in this review resulted in 409 hits. After removing duplicate studies and studies with inadequate information, 20 case studies were finally included in this analysis, 65% of which presented men (n = 13), and seven presented women (35%). The mean age reported in these studies was 54.75 with a standard deviation of 14.62 years. We found that visual disturbances that can lead to visual loss were present in most cases (75% of cases). Other symptoms included headache (35%) and eye pain (30%). The risk factors for developing optic neuropathy conditions related to OC mucoceles include being Asian and elderly with a history of either nasal or eye conditions. Our findings showed that the mean time between the onset of symptoms and intervention was 16.8 ± 21.8 days. Most patients underwent endoscopic sinus surgery to remove the OC mucocele (18/20; 90%) with a success rate of 77%. Pharmacologic intervention as a solo treatment (IV corticosteroids or /and antibiotic) was used in only

six patients, with a success rate of only 33%. Computed tomography (CT) and magnetic resonance imaging (MRI) is the most commonly used diagnostic tools, with diagnostic success rates of 40% and 82.3%, respectively. **Conclusion:** Optic neuropathy conditions related to OC mucoceles are very rare. However, a higher incidence of these conditions was observed in elderly Asian patients with a history of nasal or optic conditions. Visual disturbances are the most common symptoms accompanying any type of eye condition. Endoscopic sinus surgery is considered an effective and safe intervention for these patients, and the period between the onset of symptoms and surgery does not affect the outcomes of the surgery. Furthermore, treatment with corticosteroids and/or antibiotics cannot replace surgery and it can also worsen the condition. Moreover, MRI is superior to CT scans for demonstrating this abnormality, and both are superior to other diagnostic tools. Finally, further investigations should be conducted to study the causes of the low incidence of these conditions in the eastern region.

Keywords: Onodi cell; optic neuropathy; risk factors; CT; MRI; endoscopic surgery

1. Introduction

The Onodi cell (OC) was first described by Onodi in 1904, who defined it as an anatomic condition characterized by the projection of the posterior ethmoid within the sphenoid bone [1]. Today, it is known that OCs or sphenoethmoidal air cells are the posterior-most ethmoid air cells that undergo either superolateral, superior, or lateral pneumatization [2,3]. During normal childhood, the ethmoid and maxillary sinuses are normally found at birth. However, around seven years of age, the floor of the maxillary sinus is at the same level as the nasal floor [4]. By the age of five years, ethmoid cells start to pneumatize in the posterior direction, where the lateral and medial walls become parallel to each other, then at the age of seven, the frontal sinuses start to pneumatize; however, this is not completed until adolescence [5]. It seems that posterior ethmoid cells extend into the sphenoid bone superolaterally, surrounding the optic channel, and in most cases, an OC [6]. OCs are important for rhinology surgeons because they contain the optic canal [7], and are next to the optic nerve and internal carotid artery, with as little as 0.03 mm (median 0.08 mm) of bone separating them [8]. The prevalence of OCs, reported based on computed tomography (CT) findings, is 7% in the general population; however, a prevalence of up to 42% has been reported when the reports were not based on CT scan findings, whereas the rates are generally higher in Asian populations [9–11]. However, the difference in these rates may be due to the different diagnostic tools used rather than to the actual occurrence [12]. Due to the proximity of OCs to the optic nerve, any pathologic condition of the OC can cause devastating complications in the optic system. OC pathologic conditions include infection, mucocele, inflammatory sinusitis, fungus ball, sino-nasal malignancy, and inverted papilloma, and any of these conditions can cause visual changes because most of these conditions are not limited to OCs but extend to the osseous margins [6,13]. Mucoceles are dilated, mucus-filled cyst-like lesions that occur as a result of chronic obstruction of the sinus ostium resulting from inflammation, trauma, scarring, or obstruction [14]. Mucoceles are defined as benign lesions with expansile and cyst-like characteristics that occur in the paranasal sinuses, and their contents mostly include mucoid secretions and wrinkled respiratory epithelium [15], causing mucous secretions that plug the sinus cavity and cause enlargement of the bony sinus wall [16]. Mucoceles, although most commonly found in the frontal and anterior ethmoid sinuses, are also rarely found in the posterior ethmoid sinus [17]. Therefore, OC

mucoceles are very rare [16,18]. However, when they occur, they can cause many different eye conditions that in some cases can lead to blindness [4]. Due to the proximity of the optic nerve to OCs, OD mucoceles cause visual disorders, including loss of vision, defects of the visual field, proptosis, and extraocular palsies rather than nasal symptoms.

Although the definitive diagnosis of OC mucoceles is established intraoperatively, CT and magnetic resonance imaging (MRI) findings are also used for a preoperative diagnosis [8,19]. A coronal CT scan is important in the differential diagnosis of a mass with an osseous origin and has a greater impact in the preoperative evaluation of such findings compared to a brain CT scan, which helps identify expansile soft-tissue masses potentially found in the left anterior clinoid process, where destruction of the medial wall and the affected optic canal can be observed and potential bony erosions caused by the mucocele can also be localized [19]. On the other hand, axial and coronal MRIs are very important in the diagnosis of a mucocele in the orbital apex [4,20], where high signal intensity on T2-weighted and low intensity on T1-weighted MRI characteristically distinguish mucoceles from other masses, such as tumors. The higher protein content of the mucocele mucus may increase the T1 signal intensity on MRI, distinguishing it from the peripheral cystic walls [18,21].

Treatment of OC mucoceles can be initiated with intravenous corticosteroids and antibiotics if the infection is present; however, to our knowledge, the mechanism underlying how corticosteroids and antibiotics improve visual complications remains unclear [22]. Moreover, the most effective treatment is endoscopic surgical decompression of the mucocele, which can restore visual function [23,24].

Despite the importance of this condition, due to the rare cases of optic complications caused by isolated OC mucoceles, most of the studies that have been performed included one or two cases. Further, prospective studies have not been performed. Therefore, in this review, we aimed to explore the available data and findings of different case studies that investigated optic neuropathy related to isolated OC mucoceles. We aimed to define the different optic neuropathy conditions related to isolated OC mucoceles, determine the different symptoms and risk factors of each condition, and explore the efficacy of the diagnostic tools and treatment strategies employed.

The objectives of this study were to evaluate the risk factors related to OC mucocele-associated optic neuropathy, determine whether a patient's history or sphenoid or other nasopharyngeal conditions are considered risk factors related to OC mucocele-associated optic neuropathy, determine the effect of the interval between onset of symptoms and intervention on treatment outcomes, identify the most appropriate diagnostic tool for the diagnosis of OC mucoceles, and determine if one of the tools is superior to the other (specifically comparing the diagnostic efficacies of MRI and CT).

2. Materials and methods

2.1. Search strategy

This review was performed and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. A wide-range electronic search of studies published from 1990 to 2020 using time and language restrictions was performed in databases including PubMed, the Cochrane Library, and Web of Science.

2.2. Selection criteria

2.2.1. Inclusion criteria

Participants: Patients of any age with visual symptoms related to isolated OC mucoceles were included. Interventions included (1) any type of therapeutic intervention (pharmacological or surgical), and (2) diagnostic intervention. Studies included randomized controlled clinical trials published in English between 1990 and 2020.

2.2.2. Exclusion criteria

Trials involving patients with an optic condition related to OC pathology other than mucoceles, patients with optic neuropathy related to sphenoid mucoceles, animal studies, unsupported opinion of experts, replies to the author/editor, and conference abstracts were excluded.

2.3. Data analysis

We searched databases, such as Google Scholar, PubMed, The Cochrane Library, and Web of Science. We combined the search terms and limited the study to the English language. According to the PRISMA checklist, we removed duplicates, and the articles were screened based on title, abstract, and full text.

3. Results

3.1. Selected studies

The electronic search strategy followed in this review resulted in 409 hits, which were reduced to 312 studies after removing duplicates. Of these 312 studies, which were considered eligible for further evaluation, 285 studies were excluded for various reasons. A total of 171 studies were excluded because of inadequate title and abstract, 75 studies were not case studies, 75 studies were not relevant to the subject of this study, three were considered author replies, one was a book, three studies used craniotomy as a treatment, and 17 studies were conducted on sphenoid mucocele-caused optic neuropathy. Finally, we included 20 studies in the qualitative synthesis of the present review (Figure 1).

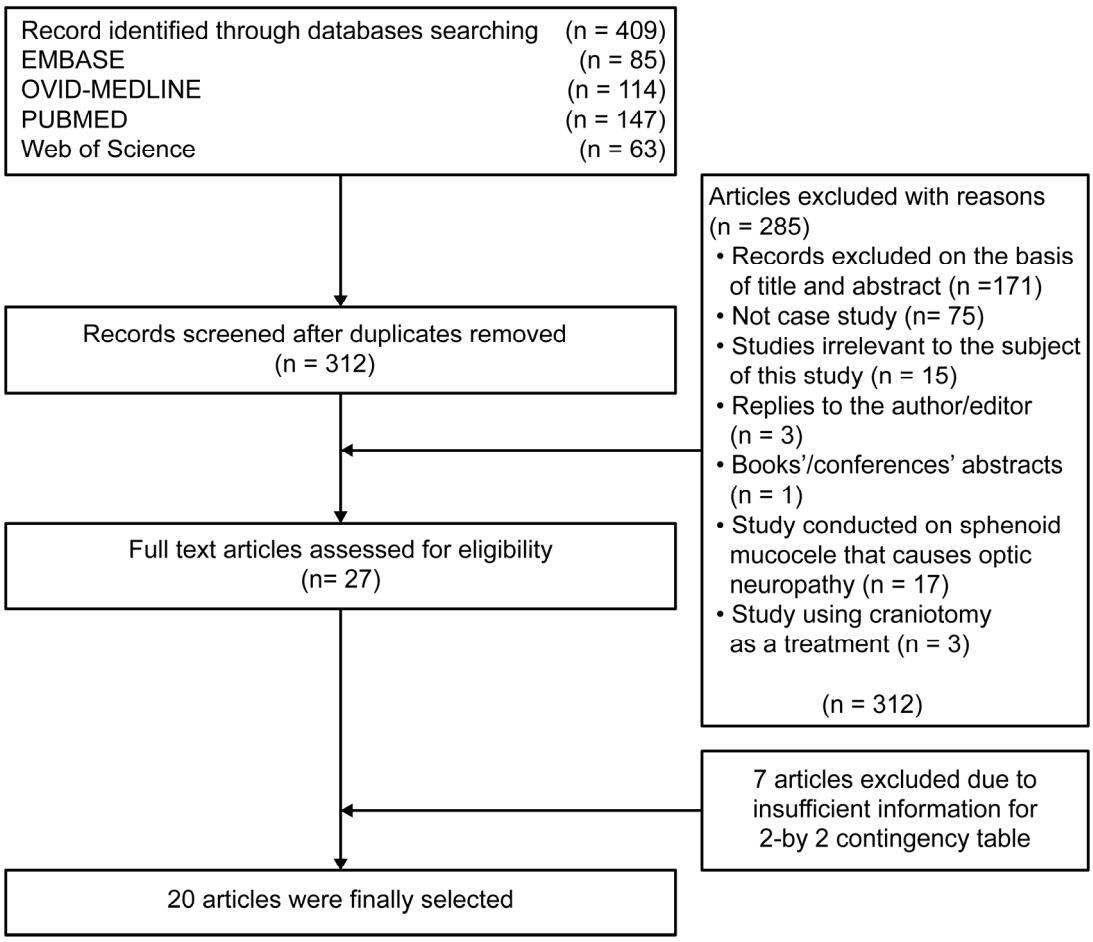

Figure 1. Flow cart (PRISMA) for choosing the studies eligible for this review.

3.2. General results

Table 1 shows the general characteristics of the 20 studies selected for this review. Due to the low incidence of the condition under review and the lack of other studies to describe it, all the studies included in this review were case studies. Each case study reviewed one case; therefore, a total of 20 cases, 65% of which were men (n = 13) and seven were women (35%). The mean age reported in these studies was 54.75 with a standard deviation of 14.62 years and an age range of 28–86 years. All the patients involved were treated at otolaryngology departments. However, the studies were conducted in different countries as follows: four studies were conducted in the USA [11,19,25,26], one in India [27], one in Greece [28], one in Germany [13], three in Japan [2,4,20], three in South Korea [8,29,30], two in Singapore [6,14], one in China [31], one in Hyogo [32], and one in Portugal [33]. Their findings were published as journal papers and/or dissertations in English between 1990 and 2020.

Table 1. General characters of studies indicating authors, type of study, location of study, summery, gender, and age.

Article	Design	Setting	General characteristics	N (M/F)
Kiyotaka Kitagawa 2003 [2]	Case study	Departments of Ophthalmology and Otolaryngology-Head and Neck Surgery Toyama Medical and Pharmaceutical University, Toyama, Japan	Optic neuropathy caused by a compressed mucocele in an OC	1 (1/0)
Yoichiro Fukuda 2006 [4]	Case study	Department of Otolaryngology-Head and Neck Surgery, Gunma University Graduate School of Medicine, Japan	Mucocele in an OC with simultaneous bilateral visual disturbance	1 (1/0)
SA Lim 2008 [6]	Case study	Department of Ophthalmology, Tan Tock Seng Hospital, Singapore	Demonstrates the rare incidence of mucocele development in the osseous structures establishing the optic canal	1 (1/0)
Kyung-Chul Yoon 2006 [8]	Case study	Department of Ophthalmology, Chonnam National University Medical School and Hospital, Gwangju, South Korea	Optic neuropathy caused by a mucocele in an OC	1 (0/1)
Andrew Victores 2012 [11]	Case study	Department of Otolaryngology-Head and Neck Surgery, Baylor College of Medicine, Houston, Texas, USA	Recurrent OC mucocele: rare cause of two different ophthalmic complications	1 (1/0)
T KLINK 2000 [13]	Case study	Department of Ophthalmology, Julius-Maximilians-University, Germany	Acute visual loss caused by an OC	1 (1/ 0)
Song-Tar Toh 2007 [14]	Case study	Department of Otolaryngology-Head and Neck Surgery, Tan Tock Seng Hospital, Singapore	OC mucoceles are a rare cause of optic compressive neuropathy	1 (1/ 0)
J. P. Nickerson 2011 [19]	Case study	Department of Otolaryngology, Johns Hopkins Medical Institute, Baltimore, MD, USA	OC mucocele causing acute vision loss	1 (0/1)
Yoichi Ogata 1998 [20]	Case study	Department of Otolaryngology, Yamaguchi University School of Medicine, Ube, Japan	Optic neuropathy caused by an isolated mucocele in an OC	1 (1/0)
JM Lee 2016 [25]	Case study	Department of Otolaryngology-Head and Neck Surgery, University of Toronto Faculty of Medicine, Toronto	OC mucocele in a 39-year-old woman, and a comprehensive review of the literature on this entity	1 (0/1)
Connor Nathe 2018 [26]	Case study	Department of Ophthalmology, University of California, Irvine School of Medicine, Irvine, CA, USA	Complete orbital apex syndrome caused by an OC mucocele	1 (0/1)

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Article	Design	Setting	General characteristics	N (M/F)
Vishal Annaji Chafale 2015 [27]	Case study	Bangor Institution of Neurosciences, Kolkata, India	Retrobulbar optic neuropathy secondary to isolated sphenoid sinus disease	1 (0/1)
Argyrios Tzamalis 2020 [28]	Case study	University of Thessaloniki, Greece	OC associated optic neuropathy	1(1/0)
Kyung Won Kwon 2019 [29]	Case study	Department of Otorhinolaryngology-Head and Neck Surgery, National Medical Center, Seoul	OC mucocele causing isolated trochlear nerve palsy	1 (1/0)
Yong-Il Cheon 2014 [30]	Case study	Department of Otorhinolaryngology and Biomedical Research Institute, San, Republic of Korea	A fungal ball within OC mucocele causing visual loss nerve palsy	1 (1/0)
Wencan Wu 2010 [31]	Case study	Eye Hospital of Wenzhou Medical College, China	Recovery of visual function in a patient with an OC mucocele causing compressive optic neuropathy	1 (1/0)
Hitoshi Fukuda 2010 [32]	Case study	Department of Neurosurgery, Hyogo	Small OC mucocele causing chronic optic neuropathy	1 (0/1)
Tiago Fuzeta Eça 2018 [33]	Case study	Otolaryngology Department, Centro Hospitalar Lisboa Norte, Hospital Santa Maria, Portugal	Surgical drainage plus optic nerve decompression in acute optic neuropathy by an OC mucocele	1 (1/0)
Efrat Fleissig 2014 [34]	Case study	Faculty of Medicine, Tel Aviv University	Blinding orbital apex syndrome	1 (0/1)
S Kashii 2016 [35]	Case study	Dept. of Ophthalmology, Osaka Red Cross Hospital, Osaka, Osaka, Japan,	Acute visual loss caused by an OC mucocele	1 (1/0)
				20 (13/7)

Note: M: Male; F: Female; OC: Onodi cell.

3.3. Results of individual studies and synthesis of the results

3.3.1. General symptoms related to neuropathic conditions and risk factors

Each study described different types of neuropathy conditions; however, all these conditions were related to the mucocele of OCs. Most patients, however, had vision loss, eye pain, headache, blurred vision, and an inability to differentiate color, and most of these symptoms had a sudden onset. Vision reduction or loss occurred in 75% of cases [2,4,8,11,14,19,20,25,26,30–34,36], while blurred vision occurred in 30% of cases [6,11,13,20,27,28] eye pain in 30% of cases [11,19,25,31,34,36], headache in 35% of cases [2,4,11,14,19,27,31], while other symptoms, such as black dots, inability to differentiate colors, and double vision, were found in some cases [13,14,29].

Considering risk factors, we found that 45% of patients with OC mucocele did not have any risk factors [8,13,20,27,28,31–33]. However, we identified other factors that may be related to this condition, including older age (the mean age of the patients was 54.75 years) and male sex (65% of the patients were male, with a ratio of 1 female to about 2 males). Furthermore, 30% of patients had a history of ENT conditions such as chronic sinusitis [11,25,34], had undergone endoscopic sinus surgery [6,11,25], tracheostomy [19], and had nasopharyngeal carcinoma [4,14]. On the other hand, 25% of patients had a history of optic conditions, including glaucoma [4,6,14], sudden blindness [36], and cataract [2]. Other risk factors include brain fracture [30], age-related macular degeneration, and bilateral pseudophakia [26]. These are shown in Table 2.

3.3.2. Effect of treatment strategies and the time interval between presentation and surgery on the final results

Table 3 presents the total time that elapsed from the onset of symptoms and treatment initiation, the treatment strategies used, and their outcomes. The mean time between the onset of symptoms and therapeutic intervention was 16.8 ± 21.8 days. No relation was found between the time from symptom onset and therapeutic intervention and the success or failure of the intervention; however, a longer period appeared to lead to worse results. Although most patients underwent endoscopic sinus surgery to remove the OC mucocele, vision could not be surgically restored in four of these patients [11,19,29,30], whereas the problems were not solved or partially solved in four of six patients who received the pharmacologic intervention (as a solo treatment with antibiotics or corticosteroids). In two patients [20,34], the usage of corticosteroids worsened the condition, considering that surgical intervention after the failure of pharmacological treatment had been successful in the four cases. Furthermore, the use of pharmacological medication in combination with or after the surgical intervention had a positive effect on the results of the surgical intervention. However, whether this affected the time to full recovery could not be determined as full recovery ranged from hours to months without having a clear pattern.

Table 2. Symptoms of conditions and related risk factors.

Article	Condition	Symptoms	Risk factors
Kiyotaka Kitagawa 2003 [2]	OC mucocele	Suddenly complained of headache and decreased vision in the left eye	Underwent cataract surgery
Yoichiro Fukuda 2006 [4]	OC mucocele	Sudden frontal headache and two-sided vision deterioration	Noncontributory except for glaucoma
SA Lim 2008 [6]	Optic neuritis because of mucocele of OC	Sudden nasal ache with the deterioration of the vision in his right eye and inability to differentiate colors	Nasopharyngeal carcinoma diagnosed and treated with radiotherapy; acute angle-closure glaucoma affecting his left eye two years ago
Kyung-Chul Yoon 2006 [8]	OC mucocele compressing the optic nerve mechanically	Acute loss of vision in the right eye	No risk factors
Andrew Victores 2012 [11]	Pacification of the right OC carefully bordering the right optic nerve	Blurred vision after the abrupt loss of vision in the right eye with eye pain and headache	CRS
T KLINK 2000 [13]	Optic neuropathy caused by an isolated mucocele in OC	Acute visual deterioration in the right eye and a central scotoma, “black dots” appeared in his central visual field	Medical and surgical history was unremarkable
Song-Tar Toh 2007 [14]	OC mucocele	Sudden onset of clouding (blurred) of vision	(1) nasopharyngeal carcinoma, 8 years earlier; (2) functional endoscopic sinus surgery 7 years earlier; and (3) chronic angle-closure glaucoma in his left eye, with decreased visual acuity for 1 year
J. P. Nickerson 2011 [19]	OC causing expansion of the bone anterior and medial to the optic canal	Unusual sensation in the eye with complete loss of vision	Left orbital fracture at the age of 13 years
Yoichi Ogata 1998 [20]	Rhinogenic optic neuropathy arising from an OC	Impaired visual acuity and blurred vision in the left eye. Sudden blindness of the left eye	Medical and surgical history was unremarkable
JM Lee 2016 [25]	OC mucocele	Pain with a progressive deterioration in visual perception in her left eye	Previous endoscopic sinus surgery
Connor Nathe 2018 [26]	Unilateral orbital apex syndrome due to an OC mucocele.	Progressive vision loss in her right eye; seeing floaters which progressed to total vision loss. No pain or trauma	Age-related macular degeneration and bilateral pseudophakia

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Article	Condition	Symptoms	Risk factors
Vishal Annaji Chafale 2015 [27]	Retrobulbar optic neuropathy	Acute visual worsening in the left eye subsequent frontal headache with no pain in her eye	Medical and surgical history was unremarkable
Argyrios Tzamalis 2020 [28]	OC mucocele associated with optic neuropathy	Sudden worsening of vision in the patient's left eye	Medical and surgical history was unremarkable
Kyung Won Kwon 2019 [29]	Trochlear nerve palsy due to an isolated mucocele in the left OC	Double vision	Medical and surgical history was unremarkable
Yong-Il Cheon 2014 [30]	Oval-shaped mass in the OC, spreading superolaterally around the left orbital apex	Headache and blindness of the left eye	No history of nasal surgery brain infarction for 5 years
Wencan Wu 2010 [31]	Compressive optic neuropathy due to an OC mucocele	Sudden decrease in right VA. Loss of vision associated with eye pain and headache	Medical and surgical history was unremarkable
Hitoshi Fukuda 2010 [32]	Onodi cell mucocele with long-term history	Gradual loss of vision over the past year	No risk factors
Tiago Fuzeta Eça 2018 [33]	Mucocele/pyocele in an OC	Progressive loss of vision in his left eye. No nasal symptoms	Medical and surgical history was unremarkable
Efrat Fleissig 2014 [34]	Blinding orbital apex syndrome	Loss of vision in her right eye accompanied by pain during eye movement	CRS
S Kashii 2016 [35]	OC mucocele	Periorbital pain around the right eye. Sudden blindness	Past medical history was notable for sudden blindness

Note: OC: Onodi cell; CRS: Chronic rhinosinusitis; VA: Visual acuity.

Table 3. Summary of time between onset of symptoms and treatment, treatment strategies used, and outcomes.

Article	Time between symptoms and treatment	Treatment	Result
Kiyotaka Kitagawa 2003 [2]	7 days	Functional endoscopic sinus surgery	VA improved eight days after surgery and complete recovery was achieved after six months
Yoichiro Fukuda 2006 [4]	NA	IV corticosteroid: methylprednisolone	VA improved but the expected recovery was not achieved
	NA	Functional endoscopic sinus surgery	VA was restored
SA Lim 2008 [6]	NA	Functional endoscopic sinus surgery	After a few days VA improved
Kyung-Chul Yoon 2006 [8]	2 days	Functional endoscopic sinus surgery, followed by IV corticosteroids	Six months after treatment, the vision improved; however, mild temporal visual field defects remained
Andrew Victores 2012 [11]	3 days	Transnasal endoscopic sphenoethmoidectomy	No improvement in VA
	6 years, the symptoms occurred again for two days	Transnasal endoscopic sphenoethmoidectomy	One week later, the right eye pain had resolved, but the vision loss persisted
T KLINK 2000 [13]	2 weeks	Functional endoscopic sinus surgery	VA improved nine days after surgery and central scotoma was reduced to small scotoma
Song-Tar Toh 2007 [14]	NA	IV antibiotic and corticosteroids	VA improved
	1 week	Functional endoscopic sinus surgery	VA improved one week after surgery
J. P. Nickerson 2011 [19]	5 weeks	Functional endoscopic sinus surgery	No improvement in VA

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Article	Time between symptoms and treatment	Treatment	Result
Yoichi Ogata 1998 [20]	NA	Corticosteroids	After four days, the symptoms worsened and blindness occurred
	2 months	Functional endoscopic sinus surgery	VA improved one week after surgery
JM Lee 2016 [25]	1 week	Functional endoscopic sinus surgery	VA improved one hour after surgery. In the first hours after surgery, the patient regained her color vision
Connor Nathe 2018 [26]	16 days	Functional endoscopic sinus surgery with optic nerve decompression	VA improved one day after surgery, with improved ocular motility in the left gaze. One week after surgery, VA was 20/20 with the improvement of extraocular movements in all gazes
Vishal Annaji Chafale 2015 [27]	2 months	The patient refused to undergo endoscopic surgery and the patient's condition was managed pharmacologically with antibiotics, mucolytics, and decongestants	VA improved one month after surgery
Argyrios Tzamalis 2020 [28]	18 hours	Transnasal endoscopic sphenoidectomy. Postoperatively, the patient was set on IV antibiotic and corticosteroids	Surgery failed to treat the deterioration in light perception, which remained unchanged through the next five days after surgery
Kyung Won Kwon 2019 [29]	3 days	Functional endoscopic sinus surgery, followed by IV corticosteroids	After two weeks, diplopia was not improved. After four months, fourth nerve palsy had completely improved
Yong-Il Cheon 201 4[30]	NA	Transnasal endoscopic sphenoethmoidectomy	No improvement in VA
Wencan Wu 2010 [31]	2 weeks	IV antibiotic and corticosteroids	After five days, the vision in the right eye improved and ocular pain and the headache disappeared
	5 weeks	Functional endoscopic sinus surgery	VA improved five days after surgery
Hitoshi Fukuda 2010 [32]	NA	Pterional-transcranial epidural approach	After surgery, the decompression of the optic canal was complete
Tiago Fuzeta Eça 2018 [33]	2 days	Functional endoscopic sinus surgery	After four days, the visual acuity improved, and after six months, the visual loss reverted completely

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Article	Time between symptoms and treatment	Treatment	Result
Efrat Fleissig 2014 [34]	one day	IV corticosteroids: methylprednisolone (1 mg/kg per day)	A few hours later, the patient had worse symptoms including diplopia, swelling in the eyelid, VA deterioration
	on the same day	Functional endoscopic sinus surgery	Eye movement was restored after surgery; however, no improvement in VA, and no light perception were observed
S Kashii 2016 [35]	NA	The patient refused surgical interventions	

Note: NA: Not applicable; VA: Visual acuity.

Table 4. Findings of the diagnostic tools used for Onodi cell mucocele diagnosis.

Article	Diagnostic tools	Efficacy	The tool success to confirm the condition
Kiyotaka Kitagawa 2003 [2]	Ophthalmic examination	Unremarkable	MRI
	CT	Opacification of the OC	
	MRI	Showed an oval-shaped lesion related to the OC that may compress the left optic nerve	
Yoichiro Fukuda 2006 [4]	Ophthalmic examination	Visual function was inadequate to light acuity in both eyes	CT
	CT	Opacification of the OC	

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Article	Diagnostic tools	Efficacy	The tool success to confirm the condition
SA Lim 2008 [6]	Ophthalmic examination	Corrected VA was 6/30 on the affected right eye and 6/12 on the left	MRI
	MRI	Revealed an opacification of OCs indicating a mucocele	
Kyung-Chul Yoon 2006 [8]	Ophthalmic examination	Unremarkable	MRI
	CT	Opacification of the OC	
	MRI	Revealed a mass with signal intensity in the right OCl compressing the right optic nerve	
Andrew Victores 2012 [11]	CT and MRI	Opacification of the OC	MRI
T KLINK 2000 [13]	Clinical presentation	Unremarkable	MRI
	MRI	Showed a kidney bean-shaped mass in the right orbital apex, which compressed the optic nerve	
Song-Tar Toh 2007 [14]	Ophthalmic examination	Failed to detect the OC opacification	CT
	CT	Revealed a mucocele in the OC	
J. P. Nickerson 2011 [19]	CT	Confirmed extension of the bone anterior to the optic canal as a result of an OC with low-density material	MRI
	MRI	Established a marginated signal extending from the OC towards the orbital canal	

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Article	Diagnostic tools	Efficacy	The tool success to confirm the condition
Yoichi Ogata 1998 [20]	CT	Failed to detect the OC opacification	MRI
	An axial CT with an 8-mm thickness	Showed no abnormal findings	
	MRI	Showed a small high-intensity area in the left OC	
JM Lee 2016 [25]	Ophthalmological examination	Edema of the left optic disc	CT
	MRI	A suspected mucocele in the left OC	
	CT	Opacification of the OC	
Connor Nathe 2018 [26]		The patient had no light perception (NLP) in the right eye. VA in the left eye was 20/50, which was later confirmed to be her baseline VA in both eyes	MRI
	CT	Opacification of the OC	
	MRI	Demonstrated an opacified right sphenoethmoidal air cell, which extended to the anterior clinoid process close to the optic nerve	
Vishal Annaji Chafale 2015 [27]	Clinical examination	Unremarkable	CT
	MRI	T2-weighted images presented high signal intensity, isointense on T1 with central hyperintense foci in the left orbital apex spreading to compress the optic nerve	
	CT	Opacification of the OC	
Argyrios Tzamalis 2020 [28]	Clinical presentation	A protruding relative afferent pupillary defect (RAPD) was noted on the left side	MRI
	Dilated fundoscopy	Was not diagnostic for optic disc edema	
	MRI	Showed a hyper-dense cystic bilobed mass in the OC	

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Article	Diagnostic tools	Efficacy	The tool success to confirm the condition
Kyung Won Kwon 2019 [29]	Ophthalmologic examination	Failed to detect the OC opacification	MRI
	MRI	Confirmed the presence of OC lesion with hypointense foci	
Yong-Il Cheon 2014 [30]	MRI	Showed an oval-shaped mass in the OC	CT
	Endoscopic examination	The nasal cavity was unremarkable	
	CT	Revealed a dense, oval-shaped mass in the OC, extending superolaterally around the orbital canal	
Wencan Wu 2010 [31]	Ophthalmic examination	Failed to suggest OC opacification	MRI
	Fundoscopy	Showed a light right optic disc	
	CT	Showed a dense mass in the OC	
	MRI	Established the presence of OC lesion that deteriorated the right optic nerve	
Hitoshi Fukuda 2010 [32]	Ophthalmological examination	Visual acuity of 20/16, 20/32 in the right and left eyes	MRI
	CT	Opacification of the OC bilaterally	
	MRI	An irregular cystic mass lesion in the OC surrounding the left optic canal	
Tiago Fuzeta Eça 2018[33]	Ophthalmologic examination	Showed a complete loss of vision on the left eye	MRI
	CT	Opacification of the OC	
	MRI	Revealed the lesion causing remodeling of the optic canal	
Efrat Fleissig 2014 [34]	Clinical examination	Swelling and erythema of the right eyelid with afferent pupillary defect	MRI
	CT	Opacification of the OC	
	MRI	Opacification of the OC	
S Kashii 2016 [35]	MRI	An oval-shaped lesion in the OC which compressed the optic nerve	CT
	CT	Opacification of the OC	

Note: OC: Onodi cell; VA: Visual acuity; CT: Computed tomography; MRI: Magnetic Resonance Imaging.

3.3.3. The efficacy of the different diagnostic tools in OC mucocele diagnosis

In the 20 studies examined in this review, physicians had used a variety of diagnostic tools, of which clinical examination, CT, and MRI scans were the most widely used. All the patients underwent a clinical examination, while 15 patients (75%) underwent a CT scan, which successfully confirmed the condition in six patients (40% diagnostic success rate). Furthermore, 17 patients underwent an MRI scan, which successfully confirmed the condition in 14 patients (82.3% diagnostic success rate). On the other hand, clinical examination failed in 25% of cases to identify the condition or remained unremarkable (Table 4).

4. Discussion

4.1. General symptoms related to neuropathic conditions and risk factors

As OC mucoceles cause optic symptoms rather than nasal symptoms, most patients with ethmoid mucoceles primarily visit the ophthalmology department rather than the rhinological department. In this review, we found that most patients (75%) had visual disturbances that could lead to vision loss. This was consistent with the findings of Loo et al. [37] and Yoo-Suk Kim et al. [38]. Furthermore, in another systematic review, all the 16 patients included in the analysis presented with a decrease in visual acuity [25]. However, the high prevalence of ophthalmologic manifestations caused by OC mucoceles, according to many studies, is underestimated [37–39]. Other symptoms noted in patients in this review include headache (35%) and eye pain (30%). Argyrios Tzamalis et al. found that pain seemed to be either headache or peri-orbital pain in 13/24 of the patients (54.2%) [28].

Regarding the risk factors related to optic neuropathy related to OC mucoceles, we found that half of the patients had no risk factors. However, this study showed that a higher prevalence of this condition is observed in Asian people than in people of other ethnicities, as 55% of the studies in this review were conducted in Asian countries [9–11]. Lee found in his review that 75% of the patients were from Asian countries [25]. Another risk factor identified in our study was older age (the mean age of patients was 54.75 years). Furthermore, 35% of the patients had a history of ENT conditions, which could be related to the history of nasal conditions and the development of OC mucocele and its complications. Furthermore, a history of optic conditions was considered a risk factor for developing optic neuropathy conditions related to OC mucoceles. Therefore, overall, our review demonstrates that the risk factors for developing optic neuropathic conditions related to OC mucoceles include Asian ethnicity, older age, and a history of either nasal or optic conditions.

4.2. The effect of treatment strategies and the time interval between presentation and surgery on the final results

It is hypothesized that surgical decompression in the early stages is critical for a good outcome. Based on this hypothesis, the time from symptom onset to the time of surgery should be minimum. In this review, however, we did not find a relationship between the time between symptom onset and surgery and the outcomes of the surgery. The mean time between the onset of symptoms and surgical intervention was 16.8 ± 21.8 days. According to Lee, the period between the onset of symptoms and surgical intervention varied from a few hours to 2 years, with no clear relation between this period and

the outcomes of surgery for vision restoration [25]. This result is also in line with the findings of the study by Yoo-Suk Kim, where no correlation was found between the two variables [38]. However, other studies confirmed the above-mentioned hypothesis; for instance, Lee et al. found that patients with optic neuropathies who underwent surgical intervention in the early stages after the onset of symptoms had improved visual outcomes compared to patients who were treated at later stages [25]. Moreover, another study by Yoon et al. showed that early-stage surgery could not improve the visual outcomes and that it may even worsen them [10], suggesting that it is difficult to accurately predict the real degree of damage that happens to the optic nerve in the early stages of the disease. Therefore, this parameter (the period between onset of symptoms and intervention) could not be considered an important variable in predicting the outcomes of intervention.

Regarding treatment strategies, most patients underwent endoscopic sinus surgery to remove the OC mucocele (18/20; 90%) with a success rate of 77%. While pharmacologic intervention as a solo treatment (IV corticosteroids or/and antibiotic) was used in only six patients, with a success rate of only 33%, the condition of two patients (33%) treated with pharmacologic intervention worsened. This is in agreement with the results of Argyrios Tzamalis [28], who indicated a decrease in visual outcomes after administration of steroids and antibiotics in the early stages. Although the treatment at first caused immediate improvement and reduced optic decompression, it did not improve visual symptoms. Therefore, the majority of the patients (21/24; 87.5%) were asked to undergo endoscopic sinus surgery (ESS), which is considered the most common treatment for OC mucoceles due to its fewer complications, less invasive nature, and quicker post-operative recovery time [23,24]. Therefore, in our review, we could not determine the role of antibiotics and corticosteroids in the treatment of OC-related optic complications.

4.3. The efficacy of the different diagnostic tools in OC mucocele diagnosis

Although the definitive diagnosis of OC mucoceles is established intraoperatively, CT and MRI findings play a great role in providing a preoperative diagnosis [4,19]. In the studies included in this review, CT and MRI were the most widely used diagnostic tools. All the patients underwent a clinical examination, while 15 patients (75%) underwent a CT scan, which successfully confirmed the condition in six patients (40% diagnostic success rate). Furthermore, 17 patients underwent an MRI scan, which successfully confirmed the condition in 14 patients (82.3% diagnostic success rate). Consistent with our results, Lee showed in his study that 13 of the 16 patients included in his review (81%) underwent both CT and MRI [25]. Therefore, axial and coronal MRI scans are valuable for distinguishing orbital apex lesions, and a coronal CT scan is useful for the differential diagnosis of a mass of an osseous origin and preoperative evaluation. However, according to our results, MRI scans have a superior ability to demonstrate this abnormality compared to CT scans.

4.4. Study limitations

This study also has some limitations. Among the most important of these is its dependence on case studies. However, as the condition reviewed here is rare, there is a lack of studies with a larger number of patients. Further, the search was limited to studies published in English. Finally, it did not include any study from Saudi Arabia or any of the Arabian countries as no studies have been conducted in these countries.

On the other hand, this study also has several advantages. The literature search was conducted in databases such as PubMed, one of the major databases for high-quality scientific research in the fields of medicine. Moreover, to the best of our knowledge, this is the first study of its type in Arabian countries. Finally, one of the advantages of this study is that it included a large number of studies published over a long period, from 1990 to 2020.

5. Conclusions

In this review, we discussed the results of 20 studies related to rare cases of Onodi cell-related optic neuropathy, finding that optic neuropathy due to Onodi cell mucocele has a higher incidence in Asian populations with risk factors, such as older age and history of nasal or optic conditions, and that visual disturbance is the most common symptom accompanying any type of optic condition.

Regarding diagnosis and treatment, we found that endoscopic sinus surgery is an effective and safe intervention for these patients; however, the period between the onset of symptoms and surgery does not affect the outcomes of the surgery. On the other hand, corticosteroids and/or antibiotics cannot replace surgery and may cause worsening of the condition. Moreover, MRI scans are superior to CT scans for detecting this abnormality, but both are superior to other diagnostic tools. Finally, further investigations should be conducted to study the causes of the low incidence of optic neuropathy related to OC mucocele in the eastern region.

Conflict of interest

The authors declare no conflicts of interest in this paper.

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