Clinical characteristics and management of orbital apex syndrome: a 10-year multicentre experience

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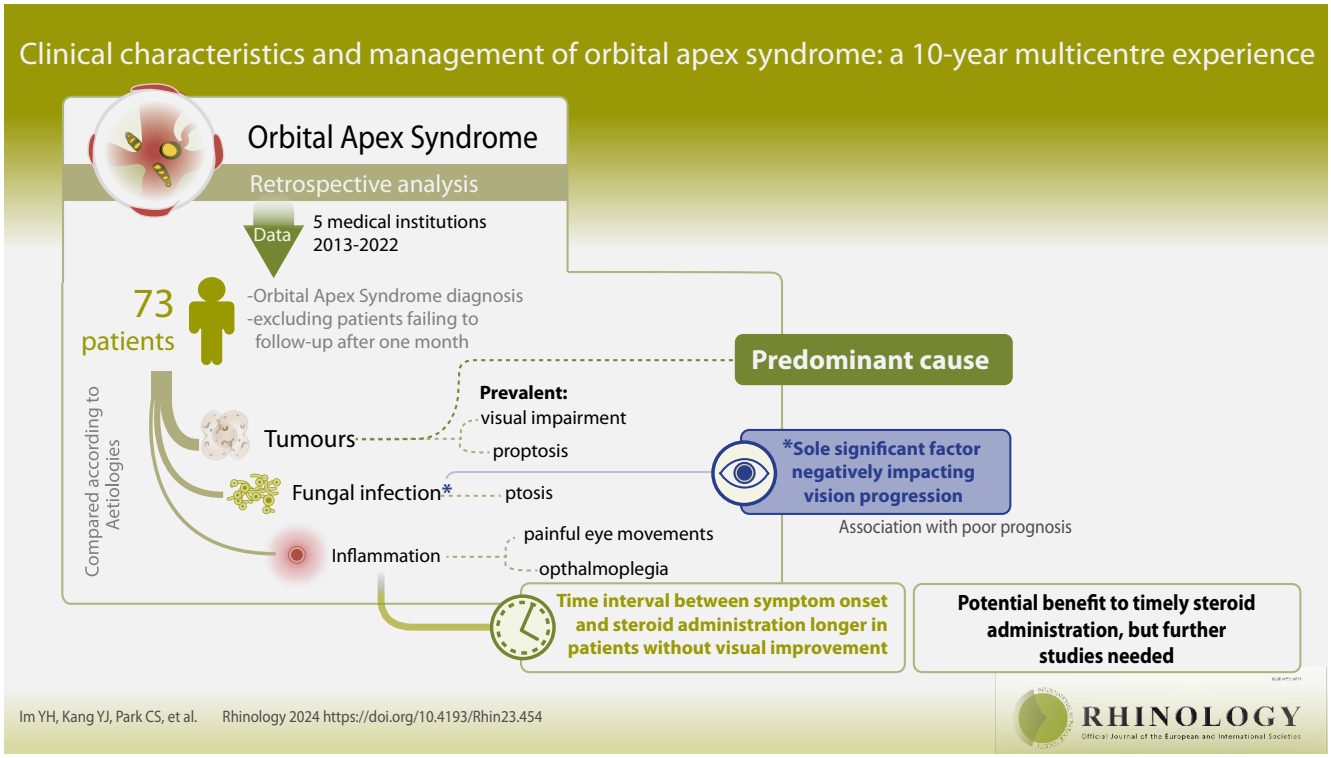

Abstract

Background: Orbital apex syndrome (OAS) is a condition characterised by lesions within the orbital apex, leading to various ophthalmologic symptoms. This study aimed to analyse the clinical characteristics and treatment strategies of OAS with respect to aetiology.

Methods: This retrospective analysis utilised data from 5 medical institutions between 2013 and 2022. Patients who were diagnosed with OAS were initially enrolled, but patients who failed to follow up at least 1 month were excluded. The prevalence of initial ophthalmologic symptoms and visual improvement after treatment was compared according to aetiology. Factors related to visual improvement were analysed.

Results: Among 73 enrolled patients, the leading aetiology was tumours, followed by fungal infections and inflammation. Visual impairment and proptosis were prevalent in tumour-related OAS cases. Inflammation-related OAS exhibited a higher likelihood of painful eye movements and ophthalmoplegia. Ptosis was most frequently observed in fungal infection-related OAS. Notably, fungal infections emerged as the sole significant factor negatively impacting vision progression. In inflammation-related OAS, the time interval between symptom onset and the administration of steroids was longer in patients without visual improvement, even though there was no statistically significant difference.

Conclusions: Tumours were the predominant cause of OAS. Visual impairment was a common manifestation in tumour-related OAS, while fungal infections were strongly associated with a poor visual prognosis. The timely administration of steroids might be helpful for improving vision in patients with inflammation-related OAS. However, further studies are needed to enhance understanding and management of OAS.

Key words: paranasal sinus diseases, sinusitis, skull base neoplasms

Introduction

Orbital apex syndrome (OAS) is a condition characterised by lesions appearing in structures of the orbital apex, leading to the involvement of cranial nerves (CNs) II, III, IV, and VI, the ophthalmic branch of the trigeminal nerve (V1), and the subsequent development of symptoms related to the affected structures [1].

Clinical manifestations and OAS severity differ depending on which structures within the orbital apex are affected [2]. The common symptoms of OAS are visual impairment and ophthalmoplegia and may additionally include periorbital pain, ptosis, mydriasis, or proptosis. However, OAS usually begins with visual impairment and ophthalmoplegia [1,3]. The orbital apex is a narrow space through which several blood vessels and nerves pass, and even minor lesions can cause clinical symptoms [4]. CNs II, III, and VI, along with the nasociliary nerve and ophthalmic artery enclosed by the annulus of Zinn, are particularly susceptible to compression or injury, resulting in visual impairment or ophthalmoplegia [5]. Ptosis can result from the impairment of either CN III, which innervates the levator palpebrae superioris muscle, or the sympathetic fibers that innervate the superior tarsal muscle [5]. Proptosis can be caused by weakened extraocular muscle tension, orbital swelling, or venous congestion [6].

The superior orbital fissure, positioned immediately in front of the orbital apex, serves as the conduit for CN III, IV, and the lacrimal, frontal, and nasociliary branches of V1. When lesions are confined to the superior orbital fissure, the optic nerve may remain intact, and visual impairment may not be present [2]. In contrast, lesions involving the cavernous sinus, located behind the superior orbital fissure, can induce sensation decrease or pain in the cheek and oculosympathetic paresis due to CN V2 and sympathetic chain involvements, respectively [5].

OAS can be caused by various aetiologies, such as inflammation, infections, vascular disorders, trauma, neoplasms, endocrine orbitopathy, and paranasal sinus mucoceles [5,7-12]. Identifying the underlying causes is important when OAS is suspected [2]. Therefore, comprehensive neuro-ophthalmologic examinations, including visual acuity, visual field, extraocular muscles, pupil reflex, ptosis, facial skin sensation, and corneal reflex tests, are essential for locating affected nerves [1,2,13]. Computerised tomography (CT) and more sensitive magnetic resonance imaging (MRI) are also important investigative tools [14]. These tools are useful for investigating the site of a lesion and making a differential diagnosis in OAS [1].

The treatment of OAS is determined by the underlying cause. Steroids are usually recommended for non-infectious inflammation-related OAS (NIOAS). However, because of the risk of relapse or exacerbation, they should be used with caution in cases of infection [2,15]. Surgical intervention is necessary for certain causes of OAS, such as those caused by orbital compartment syndrome, orbital abscess, subperiosteal abscess, or paranasal sinus mucocele [5]. Decompressive surgery or steroids are usually used to treat traumatic OAS, but their effectiveness is controversial [6,11,16].

To the best of our knowledge, the majority of previous studies on OAS have been case reports or case series, and only a few studies reported the statistical analysis of limited cases [14]. Thus, this study aimed to present the clinical manifestations and treatment outcomes of OAS according to the aetiology. We analysed the clinical characteristics of OAS and identified symptoms, disease progression, and treatment strategies (steroids, surgery, and antifungal agents) with their outcomes according to aetiology based on data from multicentre medical records and ophthalmological and radiologic findings for a decade.

Materials and methods

Patients and study design

This retrospective study utilised medical records from 5 medical institutions: Seoul St. Mary's Hospital, Incheon St. Mary's Hospital, St. Vincent's Hospital, Eunpyeong St. Mary's Hospital, and Bucheon St. Mary's Hospital. The study was approved by the Institutional Review Board of Catholic Medical Center, The Catholic University of Korea, in 2023 (approval number XC23RIDI0029), and the requirement for informed consent was waived. Permission for data usage was obtained from the ophthalmologists at each participating hospital to enroll patients treated in the ophthalmology department.

The study workflow is represented in Figure 1. Due to the absence of a specific disease code directly matched with OAS in the Korean Standard Classification of Diseases, we retrieved data on all patients (n = 6034) with diagnoses related to OAS during 10 years (at least once between January 2013 and December 2022). A comprehensive list of OAS-related disease codes and names is provided in Supplementary Table 1. Medical records and imaging studies of the patients were comprehensively reviewed by at least two authors; disagreements were resolved by involving another relevant expert in the review. Initially, 108 patients diagnosed with OAS were identified based on symptoms related to involvement of CN II, III, IV, V1, or VI (visual impairment, painful eye movement, ophthalmoplegia, or ptosis) and the presence of a lesion at the orbital apex (defined as the space between the posterior ethmoidal foramen, the superior orbital fissure, and the optic canal,) as confirmed by CT or MRI scans [17]. Patients without follow-up for a minimum of a month (n = 35) were excluded. Finally, a total of 73 patients were enrolled in the study. The overall clinical characteristics of the participants are summarised in Table 1. The mean age of the patients was 61.2

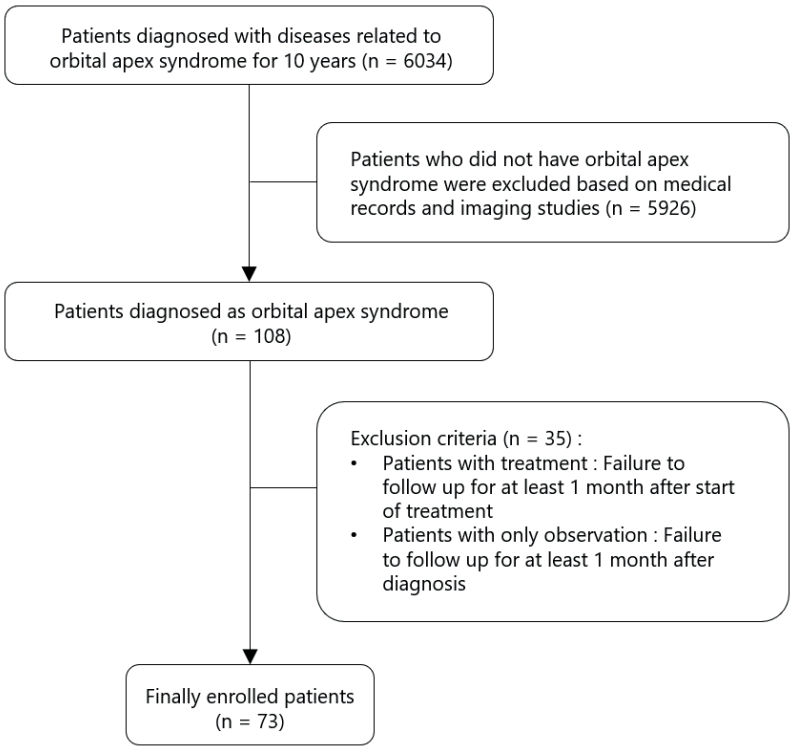

Figure 1. Study flow diagram. Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging.

years, including 35 (47.9%) males and 38 (52.1%) females.

We retrieved clinical characteristics, such as age, gender, aetiology, lesion location, presenting symptoms, and treatment approaches from all enrolled patients. We compared the proportion of each symptom based on the underlying aetiology and also examined the visual improvement in patients initially presenting with visual impairment. Aetiologies were classified based on medical records, imaging studies, and final histopathological findings. Tumour-related OAS (TOAS) category included patients histologically confirmed to have a tumour in the orbital apex and those lacking histological confirmation but exhibiting imaging evidence of tumour involvement of the orbital apex. Fungal infection-related OAS (FOAS) category included patients with histopathologically identified intratissue fungal invasion. Tolosa-Hunt Syndrome, a common cause of NIOAS, was diagnosed according to the International Classification of Headache Disorders-3 classification, which includes a unilateral periorbital headache, granulomatous inflammation of the cavernous sinus or superior orbital fissure, and palsies of CN III, IV, and/or VI that followed the headache by ≤2 weeks or developed with it, not better explained by any other aetiology [18]. Patients not exhibiting infection signs or systemic inflammatory disease but with MRI evidence of swelling and enhancement in the orbital apex were determined as having idiopathic orbital inflammation [19].

For the 3 most common aetiologies (TOAS, FOAS, and NIOAS), we assessed treatment options (steroids, surgery, and antifungal agents) as well as the time interval between symptom onset and each treatment. The timing of each treatment modality was compared between patients with and without visual improvement to investigate the factors related to visual improvement.

Ophthalmologic examination

Visual acuity was assessed using Jin's Vision Chart, which is a Korean adaptation of the LogMAR vision chart designed for a distance of 4 meters [20]. Improvement in visual acuity after treatment was defined as a transition from no light perception to light perception, from light perception to hand movement (at 1 meter), or from hand movement to counting fingers (at 10~50 centimeters). Patients who initially only distinguished optotypes corresponding to a visual acuity of 0.1 within a range of 1 to 3 meters were considered to have improved visual acuity if the distance increased by more than 1 meter after treatment. In cases where patients initially had a visual acuity of 0.1 or better, improvement was indicated when a row in which they could read 3 or more optotypes shifted by more than 2 lines following treatment. Visual field assessments were conducted using the Humphrey Field Analyzer (Carl Zeiss Meditec Inc., Dublin, CA, USA). Initial visual field impairment was determined if patients reported subjective visual field disturbances, and the mean deviation p-value was below 5% [21]. Improvement in visual

Table 1. Demographic characteristics and clinical manifestations of patients.

Factors	
Age, mean ± SD, y	61.2 ± 16.1
Gender, No. (%)	
Male	35 (48%)
Female	38 (52%)
Aetiology, No. (%)	
Tumours	28 (38%)
Cavernous venous malformation	6 (21% of tumour)
Meningioma	6 (21% of tumour)
Lymphoma	4 (14% of tumour)
Rhabdomyosarcoma	2 (7% of tumour)
Squamous cell carcinoma	2 (7% of tumour)
Others (Schwannoma, lipoma, nasopharyngeal carcinoma)	3 (11% of tumour)
Not histopathologically confirmed	5 (18% of tumour)
Fungal infection	18 (25%)
Non-infectious inflammation	13 (18%)
Tolosa-Hunt syndrome	7 (54% of non-infectious inflammation)
Idiopathic orbital inflammation	5 (38% of non-infectious inflammation)
Granulomatosis with polyangiitis	1 (8% of non-infectious inflammation)
Trauma	6 (8%)
Paranasal sinus mucocele	4 (6%)
Acute bacterial sinusitis	2 (3%)
Autoimmune disease	2 (3%)
Location of lesion, No. (%)	
Right	37 (51%)
Left	33 (45%)
Bilateral	3 (4%)
Clinical manifestations, No. (%)	
Visual acuity or visual field impairment	54 (74%)
Painful eye movement	30 (41%)
Ophthalmoplegia	45 (62%)
Ptosis	23 (32%)
Proptosis	16 (22%)
Time interval between symptom onset and	
Diagnosis, mean ± SD, d	124.5 ± 343.4
Surgery, mean ± SD, d	194.4 ± 424.9
Tumour	413.4 ± 600.3
Non-tumour	43.4 ± 83.9
Administration of steroids, mean ± SD, d	41.3 ± 59.3
Time interval between diagnosis and follow-up, mean ± SD, mo	19.4 ± 21.4
Treatment modality, No. (%)	
Steroids	29 (40%)
Surgery	49 (67%)
Endoscopic sinus surgery	26 (36%)
Craniotomy and tumour removal	11 (15%)
Orbital tumour removal (via orbitotomy or endonasal approach)	8 (11%)
Orbital wall decompression (without optic canal)	4 (5%)
Orbital wall decompression (including optic canal)	1 (1%)
Others (Open reduction of blow-out fracture, exenteration)	3 (4%)
Antifungal agent	19 (26%)
Chemotherapy	6 (8%)
Radiation therapy or concurrent chemoradiation therapy	11 (15%)
Others	2 (3%)

Abbreviations: SD, standard deviation.

field impairment after treatment was determined based on a change of at least 3 decibels in mean deviation for patients with follow-up visual field tests [22]. For those without follow-up tests, improvement was indicated if there was a subjective increase in the visual field. Extraocular muscle movements were assessed for abduction, adduction, upgaze, and downgaze. Ophthalmoplegia was diagnosed when there was a deficit of 25% or more in the maximum range of movement [23]. Proptosis was defined when the distance between the interzygomatic line and cornea exceeded 21 mm by CT (Patients without CT images were

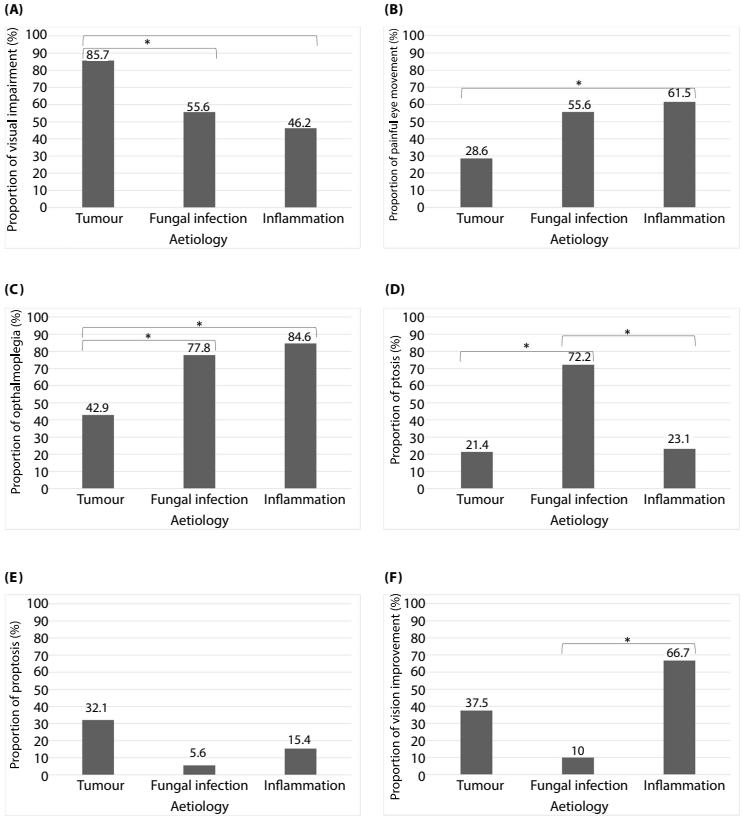

Figure 2. Proportion of each symptom and visual improvement in each aetiology. *Significant at $p < 0.05$.

evaluated using MRI images) in axial view taken at the level of the lens and the patient reported a subjective sensation of eye protrusion [24].

Statistical analysis

The data were analysed using IBM SPSS Statistics version 28 (IBM Corp., Armonk, NY, USA). Continuous variables are described as the mean with standard deviation, and categorical variables as the number and percentage of patients. The independent-samples t-test was conducted to compare normally distributed continuous variables between two groups, and the Mann-Whitney U test was conducted for non-normally distributed continuous variables. Fisher's exact test was used to compare the proportions of categorical variables between the two groups. Logistic regression analysis was utilised to determine the factors that influenced visual improvement. A p-value of < 0.05 defined significance for all tests.

Results

OAS aetiologies

Tumours (38.4%) were the most common cause of OAS in the patients, followed by fungal infections (24.7%) and non-infectious inflammation (17.8%). The tumours originated from lesions in various locations, including the orbit, paranasal sinuses, and cavernous sinus. Malignant tumours included lymphoma, rhabdomyosarcoma, squamous cell carcinoma, and nasopharyngeal carcinoma, and benign tumours included cavernous venous malformation, meningioma, lipoma, and schwannoma. Cavernous venous malformation and meningioma were the most prevalent tumour aetiologies.

Lesions were caused by invasive fungal sinusitis in all cases of FOAS, with 15 cases of aspergillosis, 2 cases of mucormycosis, and 1 case where fungal hyphae were identified in the tissue without a specific fungal type. Among NIOAS cases, one patient received a histopathological diagnosis of granulomatosis with polyangiitis, seven were diagnosed with Tolosa-Hunt syndrome, and five with idiopathic orbital inflammation. Patients with acute bacterial sinusitis presented with orbital cellulitis and ophthalmologic symptoms, and autoimmune diseases were associated with thyroid-related orbitopathy.

Clinical manifestations of OAS patients

Most patients had unilateral OAS. However, three patients with lymphoma, granulomatosis with polyangiitis, and Tolosa-Hunt syndrome were diagnosed with bilateral OAS.

The most prevalent ophthalmologic symptoms were visual

Table 2. Treatment profiles of each patient with fungal infection-related orbital apex syndrome.

No.	Gender/ age	Pathogen	Clinical symptoms	Timing from onset, days			Operation name	Visual improvement
				Anti-fungal agent	Surgery	Steroid		
1	F/72	Mucor	Visual acuity decrease, ptosis	4	5		ESS, exenteration	Not improved
2	F/73	*Aspergillus*	Visual acuity decrease, ptosis, ophthalmoplegia	18	6		ESS	Not improved
3	F/78	*Aspergillus*	Visual acuity decrease, painful eye movement, ptosis	14	1	1	ESS	Not improved
4	F/60	*Aspergillus*	Painful eye movement, ptosis, proptosis, ophthalmoplegia	9	8		ESS	
5	M/77	*Aspergillus*	Visual acuity decrease, ptosis, ophthalmoplegia	180	30		ESS	Not improved
6	M/79	*Aspergillus*	Visual acuity decrease, ptosis, ophthalmoplegia	124	124		ESS	Not improved
7	F/70	*Aspergillus*	Painful eye movement, ophthal-moplegia	8	8	10	ESS	
8	M/81	Not distinguished	Visual acuity decrease, ptosis, ophthalmoplegia	61	68		ESS	Not improved
9	F/68	*Aspergillus*	Visual acuity decrease, painful eye movement,	2	1		ESS, orbital wall decompression [a]	Not improved
10	M/74	*Aspergillus*	Ptosis, ophthalmoplegia	21	14		ESS, orbital wall decompression [b]	
11	F/80	*Aspergillus*	Ptosis, ophthalmoplegia	28	14		ESS	
12	F/82	*Aspergillus*	Visual field defect, ophthalmoplegia	12	17		ESS	Completely im-proved
13	F/74	*Aspergillus*	Painful eye movement, ptosis, ophthalmoplegia	13	7		ESS	
14	F/79	Mucor	Painful eye movement, ptosis, ophthalmoplegia	4	5		ESS	
15	F/66	*Aspergillus*	Painful eye movement, ophthalmoplegia	20	17		ESS	
16	F/55	*Aspergillus*	Painful eye movement, ptosis, ophthalmoplegia	10	5		ESS	
17	F/82	*Aspergillus*	Visual acuity decrease, painful eye movement	8	0		ESS	Not improved
18	M/82	*Aspergillus*	Visual acuity decrease, painful eye movement, ptosis	5	8		ESS	Not improved

ESS, endoscopic sinus surgery

[a] Bony optic canal decompression was also performed. [b] Bony optic canal decompression was not performed.

acuity or visual field impairment, followed by ophthalmoplegia, painful eye movement, ptosis, and proptosis. Of the 16 patients (17 eyes) meeting the criteria for proptosis, pre-treatment CT scans were available for 13 patients (14 eyes), and revealed a mean protrusion of 23.6 ± 2.4 mm from the interzygomatic line to the cornea. MRI revealed a mean protrusion of 22.2 ± 1.2 mm in the remaining three patients.

Although the average time interval between symptom onset and surgery was about 8 months, patients with TOAS showed longer time intervals (about 13.5 months) than patients with other aetiologies (about 1.5 months). The main treatment modalities in this study were the administration of steroids (29 patients), antifungal agents (19 patients), and surgical procedures (49 patients). However, cyclophosphamide was used to treat granulomatosis with polyangiitis, and rituximab was administered for lymphoma.

The clinical manifestations of FOAS patients are summarised in Table 2. All patients underwent endoscopic sinus surgery.

Table 3. Treatment modalities for the 3 common aetiologies.

	Tumour (n = 28)	Fungal infection (n = 18)	Non-infectious inflammation (n = 13)
Steroids, No. (%)	6 (21%)	2 (11%)	13 (100%)
Surgery, No. (%)	20 (71%)	18 (100%)	1 (8%)
Antifungal agent, No. (%)	0 (0%)	18 (100%)	0 (0%)
Time interval between symptom onset and			
Administration of steroids, mean ± SD, d	65.7 ± 102.3	5.5 ± 6.4	45.4 ± 44.3
Surgery, mean ± SD, d	413.4 ± 600.3	18.8 (30.6%)	65.0
Administration of antifungal agent, mean ± SD, d	NA	30.1 (47.3)	NA

Abbreviations: SD, standard deviation; NA, not available.

Table 4. Factors contributing to visual improvement.

Logistic regression analysis	Total study group OR (95% CI)	P	Tumour OR (95% CI)	P	Non-infectious inflammation OR (95% CI)	P
Age	1.019 (0.974-1.065)	0.418	0.959 (0.895-1.026)	0.226	1.066 (0.928-1.224)	0.366
Male	0.289 (0.080-1.046)	0.059	0.508 (0.074-3.464)	0.489	2.657 (0.035-200.556)	0.658
Fungal infection	0.051 (0.004-0.689)	0.025 [a]				
Administration of steroids	1.154 (0.254-5.231)	0.853	0.808 (0.029-22.581)	0.900		
Surgery	1.677 (0.370-7.598)	0.503	1.418 (0.116-17.323)	0.784		

	Patients with visual improvement	Patients without visual improvement	P	Patients with visual improvement	Patients without visual improvement	P	Patients with visual improvement	Patients without visual improvement	P
Time interval between symptom onset and									
Administration of steroid, mean ± SD, d	31.7 ± 39.6	52.4 ± 88.4	0.661	30.0	112.7 ± 139.1	0.655	15.6 ± 12.0	88.0 ± 73.5	0.064
Surgery, mean ± SD, d	267.2 ± 409.0	219.8 ± 504.6	0.373	471.3 ± 478.0	447.8 ± 756.3	0.329			
Treatment of tumour removal (surgery, chemotherapy, or radiation), mean ± SD, d				415.8 ± 469.6	355.3 ± 633.8	0.413			

Abbreviations: OR, odds ratio; CI, confidence interval; SD, standard deviation. [a] Significant at $p < 0.05$.

In addition, patient No. 1 underwent exenteration, patient No. 9 underwent decompression of the medial orbital wall with bony optic canal, and patient No. 10 underwent medial orbital wall decompression (not including bony optic canal). Only one patient (patient No. 12) demonstrated improved vision among the patients who initially showed visual impairment.

Ophthalmologic symptoms and visual improvement depending on aetiology

Figure 2 shows a comparison of various ophthalmologic symptoms according to the 3 main aetiologies: TOAS, FOAS, and NIOAS. TOAS showed the highest prevalence of visual impairment (85.7%) and proptosis (32.1%). Conversely, NIOAS patients showed the highest prevalence of painful eye movement (61.5%) and ophthalmoplegia (84.6%). Significant differences were seen in the proportions of painful eye movement in TOAS and NIOAS ($p = 0.044$) and in the proportions of ophthalmoplegia in TOAS and the other aetiologies ($p = 0.020$ compared to FOAS and 0.012 compared to NIOAS). Ptosis predominantly developed in FOAS (72.2%), which was a significant difference compared to TOAS ($p = 0.001$) and NIOAS ($p = 0.007$).

Among the 54 patients with initial symptoms of impaired vision, only 20 (37.0%) demonstrated visual improvement following treatment. Although the proportion of patients with visual improvement varied by aetiology, NIOAS showed the highest

improvement rate (66.7%), followed by TOAS (37.5%), whereas FOAS had the lowest rate (10.0%) among the 3 common aetiologies. A statistically significant difference in the proportion of patients with visual improvement was seen between FOAS and NIOAS (p = 0.036).

Visual improvements depending on treatment modality

The percentage of treatment modalities used and the time to each treatment in the 3 main aetiologies (TOAS, FOAS, and NIOAS) are summarised in Table 3. The majority (71.4%) of TOAS patients underwent surgery, with an average time interval between symptom onset and surgery of 413.4 days. Among the TOAS patients, 5 underwent orbitotomy, 3 underwent endonasal orbital surgery, and 11 patients underwent craniotomy, for tumour removal. Additionally, a patient with an orbital lipoma received a combined treatment of medial-inferior orbital decompression (excluding the bony optic canal) and anterior orbitotomy for tumour removal. Furthermore, one meningioma patient underwent the tumour removal through both endonasal and craniotomy approaches. All FOAS patients underwent endoscopic sinus surgery and then received antifungal agents, with average time intervals of 18.8 and 30.3 days, respectively. Only two FOAS patients were treated with steroids. In a FOAS patient with visual impairment and a relative afferent pupillary defect, methylprednisolone was administered intravenously from an initial dose of 1000 mg and was tapered for about 1 month. In the other patient without visual impairment but with a relative afferent pupillary defect, prednisolone was administered orally from an initial dose of 40 mg and tapered for 24 days.

Patients with NIOAS received various doses and durations of steroids, with initial doses ranging from 20 mg of peroral prednisolone to intravenous methylprednisolone at 1000 mg. The average time interval between symptom onset and the administration of steroids was about 1.5 months. Only 1 patient with Tolosa-Hunt syndrome had endoscopic sinus surgery for sphenoid sinusitis.

Table 4 presents the results of the logistic regression analysis and a comparison of the time interval to each treatment modality between patients with and without visual improvement to identify factors related to visual improvement. In the overall study group, although age, gender, steroid administration, and surgery had no effect on visual improvement, fungal infection was identified as a significant negative factor (p = 0.025). The time interval to each treatment modality had no significant effect on visual improvement. In TOAS patients, age, gender, steroid administration, surgery, and the time interval to each treatment did not show significant differences in visual improvement. In NIOAS patients, although the time interval between symptom onset and the administration of steroids was different between patients with and without improved vision, the differences were not statistically significant (15.6 versus 88.0 days, p = 0.064). Therefore, in NIOAS patients, no factors were significantly associated with visual improvement.

In the fungal infection subgroup, visual improvement was observed in only one patient and thus was not suitable for further statistical analysis.

Discussion

OAS is a condition characterised by orbital apical lesions that involve cranial nerves and cause a variety of ophthalmologic symptoms, of which ophthalmoplegia and visual impairment are the main clinical features of OAS. In this study, we analysed the clinical characteristics of OAS and investigated treatment modalities and factors related to vision and prognosis based on 10-year multicentre data.

In our study, the average age of the entire study cohort was 61.2 years, with a male-to-female ratio of 35:38. The most predominant cause of OAS was tumours, followed by fungal infections and non-infectious inflammation. Previous studies reported a mean patient age of 47 – 65 years and a male predominance in OAS cohorts [13,14]. Like previous studies, tumours were also the main cause of OAS, and the most common symptom was visual impairment (74.0%), followed by ophthalmoplegia, painful eye movement, ptosis, and proptosis in our study [13,14,25].

As shown in Figure 2, among the 3 main aetiologies (TOAS, FOAS, and NIOAS), TOAS had the highest prevalence of visual impairment and proptosis. Although lymphoma is not a solid tumour that directly involves the optic or cranial nerves in the orbital apex, it can result in OAS as compartment syndrome because the orbital apex is a closed space [14].

Painful eye movement and ophthalmoplegia were the primary symptoms in patients with NIOAS. This corresponds to the definition of Tolosa-Hunt syndrome, which accounted for 46.2% of NIOAS cases in our study and is characterised by granulomatous inflammation, CN III, IV, or VI paresis, and periorbital pain [18,26]. Ptosis was the most prevalent symptom in FOAS patients. Out of 54 patients with initial visual impairment, 37.0% showed improvement after treatment. However, in contrast to our results, Lee et al. reported that 29% of patients with initial visual impairment experienced improvement, 21% showed no change, and 50% worsened [13]. Although visual impairment was most common in TOAS patients, fungal infections showed the poorest prognosis for vision after treatment in our study, which suggests that it is necessary to inform FOAS patients that the final prognosis for vision might be poor even with appropriate treatment.

However, our results were different from the results of a previous

study that showed TOAS was associated with poor initial vision and a poor vision prognosis after treatment [13]. A study by Aryasit et al. reported that the aetiology of OAS and vision prognosis after treatment were not significantly related to each other [14].

Although the time interval between symptom onset and surgery was 194.4 days in our study, the TOAS interval was significantly longer (average of 413.4 days) than that of non-tumour OAS (average of 43.4 days). The reasons for the delayed diagnosis and treatment of TOAS might be the gradual onset of symptoms and slow disease progression. The need to carefully consider the risks and benefits of surgical intervention might have further delayed the timing of treating TOAS patients.

TOAS treatment strategies vary according to tumour type. The most common orbital tumour, cavernous venous malformation, requires surgical removal in cases of symptomatic disease, optic nerve compression, and deforming proptosis [27]. Optic nerve sheath meningioma tends to grow slowly over several years, with observation recommended for small lesions with functional vision [28]. Surgery is not recommended due to the risk of iatrogenic blindness, except in cases of deforming proptosis with severe visual impairment or intracranial extension [28]. For benign orbital peripheral nerve sheath tumours, such as neurofibromas and schwannomas, complete surgical excision or radiation therapy is performed [29]. When the surgical resection of orbital tumours is not possible, orbital decompression or optic nerve decompression has been suggested as alternative strategies to preserve or improve visual function [29-31].

In our study, it was difficult to analyse the effects of steroids, surgery, or treatment timing on visual improvement in patients with FOAS because only 1 patient showed visual improvement. The reasons for this might have been due to a delay in visiting the hospital after symptom onset and a delayed consult with an otolaryngologist for suspected fungal sinusitis. However, vision did not improve even in a patient who received immediate surgery on the day of symptom onset. Invasive fungal sinusitis is rare but shows aggressive progression and high mortality rates [32,33]. Early surgical intervention and the prompt administration of antifungal agents upon diagnosis are crucial for effective treatment [33-35]. However, how emergently surgery should be performed is still controversial [34]. Patients with rhino-orbital-cerebral mucormycosis who underwent surgery within 1 – 6, 7 – 12, and 13 – 30 days did not have significantly different survival rates [36]. In contrast, the early administration of antifungal agents within 12 days was associated with improved survival (61% versus 33%) [36].
Steroids have the potential to exacerbate immunosuppression and favor fungal growth [37]. Nevertheless, steroids are often administered to patients with fungal infections with optic neuropathy to reduce perineural inflammation and swelling [38]. Further research is needed to determine whether steroid administration can be beneficial for improving vision in invasive fungal sinusitis accompanied by optic neuropathy, such as in OAS.

Steroids were administered to all patients who had an inflammatory aetiology. A difference in the time interval for steroid administration between patients with and without visual improvement was suggested (15.6 versus 88.0 days, $p = 0.064$). The study suggests that early steroid administration may be necessary for complete vision restoration in NIOAS patients and recommends corticosteroids as the primary treatment option for these patients [2]. Immunomodulatory therapy could also be helpful for idiopathic orbital inflammation (39). Idiopathic orbital inflammation is an inflammatory condition of unknown origin that typically responds well to systemic steroids (40). Similarly, Tolosa-Hunt syndrome, a variant of idiopathic orbital inflammation, is characterised by a prompt response to steroids [41]. Although there is no consensus on the optimal dosage or duration of steroid therapy, tapering is usually done over several weeks to months [7].

This study identified tumours as the most common cause of OAS, followed by fungal infection and non-infectious inflammation. Visual impairment was common in tumour-related OAS, while fungal infection had the poorest visual prognosis after treatment. Ptosis was prevalent in fungal infections. Treatment timing did not significantly impact visual improvement in patients with tumour-related OAS. Fungal infection adversely affected visual prognosis, even with prompt antifungal agent and surgery.

Our study also had a few limitations. First, this was a retrospective chart review based on 10-year multicentre data. Selection bias may have been present due to the limitations of retrospective data and unreliable patient recall [42]. Second, the relatively small sample sizes for each aetiological subgroup made statistical analysis difficult because OAS itself is a rare condition [2]. Third, treatment plans might have been inconsistent depending on the department dedicated to OAS patients, such as otolaryngology, ophthalmology, neurology, and emergency medicine. However, to the best of our knowledge, our study was the first organised statistical analysis conducted on the largest number of OAS subjects based on multicentre data. Further studies are needed to determine the best treatment strategies, timing, and dosages for OAS patients.

A significant proportion of patients presenting with OAS had origins in sinonasal cavity disorders, often requiring the use of an endonasal approach to access the orbital apex or cavernous sinus. Moreover, in FOAS patients, urgent treatment is impe-

rative. However, diagnosis delays are frequently encountered due to late referrals to the otolaryngology department. This underscores the necessity of involving otolaryngologists, in collaboration with neurologists and ophthalmologists, in the comprehensive care of individuals suspected to have OAS. Consequently, otolaryngologists should actively strive to expand their understanding of OAS and actively participate in research related to this condition.

Conclusion

Tumours emerged as the leading aetiology for OAS, followed by fungal infections and inflammation. Visual impairment was predominant in cases of tumour-related OAS, while fungal infections were associated with the least favorable post-treatment visual outcomes as a single significant negative factor. Early steroid therapy is recommended for patients with NIOAS. Further research is needed to understand and treat this rare condition with proper protocols.

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Conflicts of interest

No authors have had financial benefits or any other relationship that could create conflicts of interest.

Authors' contributions

YHI: Conceptualization, software, validation, visualization, writing - original draft preparation, review and editing; YJK: Formal analysis, writing - original draft preparation, review and editing; DHK, YCK, JSK, HR, SHP, DWB, HRY, YWC, SHH: Data curation; CSP: Conceptualization, methodology, data curation, writing—review and editing, supervision; All authors have read and agreed to the published version of the manuscript.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

References

1. Yeh S, Foroozan R. Orbital apex syndrome. Curr Opin Ophthalmol. 2004; 15(6): 490-498.
2. Badakere A, Patil-Chhablani P. Orbital apex syndrome: a review. Eye Brain. 2019; 11: 63-72.
3. Ing EB, Purvin V. Progressive visual loss and motility deficit. Surv Ophthalmol. 1997; 41: 488-492.
4. Gupta R, Khan YA. Traumatic orbital apex syndrome. Can J Ophthalmol. 2015; 50: e8-e11.
5. Goyal P, Lee S, Gupta N, et al. Orbital apex disorders: imaging findings and management. Neuroradiol J. 2018; 31: 104-125.
6. Bun RJ, Vissink A, Bos RR. Traumatic superior orbital fissure syndrome: report of two cases. J Oral Maxillofac Surg. 1996; 54: 758-761.
7. Kline LB, Hoyt WF. The Tolosa-Hunt syndrome. J Neurol Neurosurg Psychiatry. 2001; 71: 577-582.
8. Bachman Groth JA, Harris GJ. Case report: idiopathic sclerosing orbital inflammation. Optom Vis Sci. 2021; 98: 409-417.
9. Lim JJ, Ong YM, Wan Zalina MZ, Choo MM. Herpes Zoster ophthalmicus with orbital apex syndrome-difference in outcomes and literature review. Ocul Immunol Inflamm. 2018; 26: 187-193.
10. Leferman CE, Ciubotaru AD, Ghiciuc CM, Stoica BA, Gradinaru I. A systematic review of orbital apex syndrome of odontogenic origin: proposed algorithm for treatment. Eur J Ophthalmol. 2021; 31: 34-41.
11. Talwar AA, Ricci JA. A meta-analysis of traumatic orbital apex syndrome and the effectiveness of surgical and clinical treatments. J Craniofac Surg. 2021; 32: 2176-2179.
12. Yuan M, Tandon A, Li A, et al. Orbital apex syndrome secondary to invasive Aspergillus infection: a case series and literature review. J Neuroophthalmol. 2021; 41: e631-e638.
13. Lee PH, Shao SC, Lee WA. Orbital apex syndrome: a case series in a tertiary medical center in Southern Taiwan. Front Med (Lausanne). 2022; 9: 845411.
14. Aryasit O, Preechawai P, Aui-Aree N. Clinical presentation, etiology and prognosis of orbital apex syndrome. Orbit. 2013; 32: 91-94.
15. Robinson D, Wilcsek G, Sacks R. Orbit and orbital apex. Otolaryngol Clin North Am. 2011; 44: 903-922, viii.
16. Zhou G, Yu B, Tu Y, Shi J, Wu W. endoscopic transethmosphenoid optic canal and orbital apex decompression for patients with traumatic orbital apex syndrome. J Craniofac Surg. 2020; 31: 214-218.
17. Ettl A, Zwrtek K, Daxer A, Salomonowitz E. Anatomy of the orbital apex and cavernous sinus on high-resolution magnetic resonance images. Surv Ophthalmol. 2000; 44: 303-323.
18. Headache Classification Committee of the International Headache Society (IHS). The international classification of headache disorders, 3rd edition. Cephalalgia. 2018; 38: 1-211.
19. Mombaerts I, Bilyk JR, Rose GE, et al. Consensus on diagnostic criteria of idiopathic orbital inflammation using a modified delphi approach. JAMA Ophthalmol. 2017; 135: 769-776.
20. Jin YH. A new LogMAR vision chart: Jins vision chart. J Korean Ophthalmol Soc. 1997; 38: 2036-2044.
21. Millis RP. Statistical aids to visual field interpretation. J Ocul Phalmacol. 1991; 7: 89-95.
22. Musch DC, Gillespie BW, Palmberg PF, Spaeth G, Niziol LM, Lichter PR. Visual field improvement in the collaborative initial glaucoma treatment study. Am J Ophthalmol. 2014; 158: 96-104. e2.
23. Kang MS, Yang HK, Kim NJ, Hwang JM. Clinical features of ocular motility in idiopathic orbital myositis. J Clin Med. 2020; 9: 1165.
24. Naik MN, Tourani KL, Sekhar GC, Honavar SG. Interpretation of computed tomography imaging of the eye and orbit, a systematic approach. Indian J Ophthalmol. 2002; 50: 339-353.
25. Brovkina AF, Val'skiĭ VV. [Orbital apex syndrome]. Vestn Oftalmol. 1989; 105: 49-52.
26. Kim H, Oh SY. The clinical features and outcomes of Tolosa-Hunt syndrome. BMC Ophthalmol. 2021; 21: 237.
27. Calandriello L, Grimaldi G, Petrone G, et al. Cavernous venous malformation (cavernous hemangioma) of the orbit: current concepts and a review of the literature. Surv Ophthalmol. 2017; 62: 393-403.
28. Eddleman CS, Liu JK. Optic nerve sheath meningioma: current diagnosis and treatment. Neurosurg Focus. 2007; 23: E4.
29. Sweeney AR, Gupta D, Keene CD, et al. Orbital peripheral nerve sheath tumors. Surv Ophthalmol. 2017; 62: 43-57.
30. Kloek CE, Bilyk JR, Pribitkin EA, Rubin PA. Orbital decompression as an alternative management strategy for patients with benign tumors located at the orbital apex. Ophthalmology. 2006; 113: 1214-1219.
31. Maza G, Subramaniam S, Yanez-Siller JC, Otto BA, Prevedello DM, Carrau RL. The role of endonasal endoscopic optic nerve decompression as the initial management of primary optic nerve sheath meningiomas. J Neurol Surg B Skull Base. 2019; 80:

568-576.
32. Waitzman AA, Birt BD. Fungal sinusitis. J Otolaryngol. 1994; 23: 244-249.
33. Craig JR. Updates in management of acute invasive fungal rhinosinusitis. Curr Opin Otolaryngol Head Neck Surg. 2019; 27: 29-36.
34. Deutsch PG, Whittaker J, Prasad S. Invasive and non-invasive fungal rhinosinusitis-a review and update of the evidence. Medicina (Kaunas). 2019; 55: 319.
35. Valera FC, do Lago T, Tamashiro E, Yassuda CC, Silveira F, Anselmo-Lima WT. Prognosis of acute invasive fungal rhinosinusitis related to underlying disease. Int J Infect Dis. 2011; 15: e841-e844.
36. Vaughan C, Bartolo A, Vallabh N, Leong SC. A meta-analysis of survival factors in rhino-orbital-cerebral mucormycosis-has anything changed in the past 20 years? Clin Otolaryngol. 2018; 43: 1454-1464.
37. Patterson TF, Thompson GR, 3rd, Denning DW, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the infectious diseases society of America. Clin Infect Dis. 2016; 63: e1-e60.
38. Stunkel L, Van Stavern GP. Steroid Treatment of Optic Neuropathies. Asia Pac J Ophthalmol (Phila). 2018; 7: 218-228.
39. Espinoza GM. Orbital inflammatory pseudotumors: etiology, differential diagnosis, and management. Curr Rheumatol Rep. 2010; 12: 443-447.
40. Rachwani-Anil R, Zamorano-Martín F, Rocha-de-Lossada C, et al. Orbital inflammatory disease. Arch Soc Esp Oftalmol (Engl Ed). 2022; 97: 89-99.
41. Weber AL, Romo LV, Sabates NR. Pseudotumor of the orbit. Clinical, pathologic, and radiologic evaluation. Radiol Clin North Am. 1999; 37: 151-168, xi.
42. Geneletti S, Richardson S, Best N. Adjusting for selection bias in retrospective, case-control studies. Biostatistics. 2009; 10: 17-31.

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