

Optic Perineuritis and its Association with Rheumatic Connective Tissue Disease

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Research article

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Abstract

Objective Analyze the etiology and clinical characteristics of optic perineuritis (OPN) in a Chinese patient population

Methods Neuro-ophthalmological examination and a series of blood samples were used in this retrospective observational cohort study to compare characteristics of OPN with idiopathic demyelination optic neuritis (IDON).

Results 44 OPN cases (74 eyes) and 61 IDON cases (78 eyes) were analyzed. The causes of OPN with CTD were Graves' disease, Immunoglobulin G4-related disease (IgG-4 RD), granulomatosis with polyangiitis (GAP), systemic lupus erythematosus (SLE), Sarcoidosis, Rheumatoid, scleroderma, Behcet's disease, and gout. Overall, 33 cases showed orbit fat infiltration. Specifically, 9 cases with IgG-4 RD showed trigeminal nerve branch involvement, 12 cases with Graves' showed extraocular muscle belly enlargement, and 4 cases with GAP showed pterygopalatine fossa pseudotumor through orbital magnetic resonance imaging (MRI). Compared to IDON patients, OPN patients were older ($p=0.004$) and more likely bilateral involvement 26 (78.79%) patients had bilateral involvement in OPN group versus 17 (27.87%) in the IDON group ($p<0.001$). Visual acuity scores was better in OPN patients compared to those with IDON, 0.55 ± 0.91 versus 1.19 ± 1.24 ($p<0.001$). 8 (13.11%) IDON patients also had multiple sclerosis (MS) and 7 (11.48%) patients had neuromyelitis which was significantly more than the 0 patients in OPN group ($p=0.04$).

Conclusions OPN had distinct etiologies and clinical characteristics from IDON and is more often associated with rheumatic CTD. Using OPN characteristics to diagnose CTD should prove useful for clinicians when presented with patients that have multiorgan dysfunction that include ophthalmologic findings.

Introduction

Optic perineuritis (OPN) is a rare form of orbital inflammatory disease targeting the optic nerve sheath (1). OPN usually presents with minor visual impairment, optic disc edema, and visual field abnormalities that include arcuate defects and peripheral island defects (2). OPN mimics optic neuritis but is distinguished by the classical optic nerve sheath (ONS) enhancement observed on MRI (3). OPN has long been considered an idiopathic inflammatory disease. However, recent reports suggest it may be related to other inflammatory and infectious diseases (4), yet most studies are case reports and lack a detailed analysis of OPN pathogenesis and clinical features.

OPN is a special optic neuropathy that has a distinct etiology from neuromyelitis optica spectrum disorders (NMOSDs) or multiple sclerosis (MS)-related optic neuritis (ON). Prior studies often found OPN associated with rheumatic connective tissue diseases (CTDs) (5), yet its pathogenic mechanisms are still unclear. OPN differs from idiopathic demyelination optic neuritis (IDON) which is caused by demyelinating of the optic nerve due to inflammation(6). Optic nerve sheath biopsy from a prior study showed, thickening of the perioptic meninges and the pia mater due to fibrosis and inflammatory infiltration, without vasculitis or granulomas, yet mechanisms of how this inflammation developed and invaded the nerve sheath remain unknown(1).

In this study of 44 Chinese patients with OPN, we examine the most common etiologies and using patient imaging data, try to elucidate mechanisms underlying OPN related to connective tissue diseases.

Materials And Methods

1. Patients

44 patients with OPN were recruited from the ophthalmology department of Beijing Friendship Hospital (BFH) at Capital Medical University, in Beijing, China. Patient recruitment took place from September 2015 to November 2018, and patients meeting the inclusion criteria were offered participation in the study, which included consultation and follow-up outpatient visits. Inclusion criteria were contrast enhancement surrounding the intra-orbital optic nerve and at least one of the following clinical symptoms: 1) reduction of visual acuity, 2) impairment of visual field, or 3) eye pain(1, 2). Patient follow-up varied, lasting from 6–36 months. Exclusion: MRI contrast enhancement or T2 lesions of the intra-orbital optic nerve.

2. Neuro-ophthalmological Examination

Ophthalmic examinations included slit lamp examination, pupillary reaction testing, noncontact intraocular pressure examination, and fundus examination by senior neuro-ophthalmologists. Visual acuity was examined using the standard table of vision logarithms at a distance five meters. Those unable to read any letters at one meter were further examined using finger counts, hand movements, or light perception. Visual field testing was performed using a Humphrey field Analyzer (30 – 2 SITA, Humphrey 750i, Zeiss, Germany). Optical coherence tomography (OCT) examinations were performed using enhanced depth imaging (EDI) and OCT (Spectralis; Heidelberg Engineering, Heidelberg, Germany).

Orbital MRI was performed in all patients and evaluated using MRI-3.0T (TW1WSPEED HDXT, GE, USA). Scanning sequence and parameters included coronal T1-weighted Fast spin-echo (TR = 660 ms; TE = 11.1 ms, matrix size = 256 × 256 mm, FOV = 18 × 18 cm, slice thickness = 3.0 mm) and Gd-DTPA 0.1 mmol/kg was used as contrast agent for enhanced MRI when combined with a fat suppression scan technique. We took care to not mistake normal dural enhancement due to the rich vascular supply of the region by looking for the “tram-track sign”. Two senior radiologists reviewed the MRI images as necessary.

Serum was drawn at the Examination Center for Biomedical Research of BFH. Blood samples were collected as part of routine treatment for this study.

3. Statistical Analysis

Cohort differences in age and visual acuity were analyzed using the Mann-Whitney test, Pearson χ^2 tests, or Fisher's exact test were used to control for gender, clinical symptoms, prognosis, and bilateral involvement. All statistical analyses were performed using Statistical Package for the Social Sciences software V.19.0 (IBM Corporation). Statistical significance was defined as $p < 0.05$.

4. Ethics Approval And Consent To Participate

This study was approved by the BFH Ethics Committee and was conducted following the latest iteration of the Declaration of Helsinki (version:2019-P2-201-01). Participants were given written informed consent (version V1.1/2019-09-16) before inclusion in the study.

Results

1. Demographics and clinical characteristics

44 patients (23 males and 21 females) had unilateral or bilateral OPN which included a total of 74 eyes. Age at OPN diagnosis ranged from 26 to 64 years (mean \pm SD: 52.64 \pm 17.42). A summary of the demographics of our population can be found in Table 1. Notable ophthalmologic findings include 11 patients with ptosis, 9 patients with diplopia, and 10 patients with exophthalmos. Visual field abnormalities included irregular defects 27 (52.94%), peripheral island defects 16 (31.37%) and diffuse visual field defect 8 (15.69%). The optic disc was swollen in 55 eyes and MRI showed enhancement of the optic nerve sheath in all cases (Figure 1).

2. OPN etiologies

CTDs and infectious diseases were the main causes of the OPN (Figure 2). In line with previous reports, we found OPN in patients with Graves' disease (12), IgG-4 (10), GPA (4), SLE (2), sarcoidosis (1), rheumatoid disease (1), scleroderma (1), Behcet's disease (1), gout (1), tuberculosis (5), sparganosis (1), ocular toxoplasmosis (1), bacterial meningitis (1), fungal meningitis (1), and cytomegalovirus (1), as well as one patient diagnosed with idiopathic inflammation (Table 1).

3. Differences between OPN and IDON

We compared OPN and IDON in Table 2. OPN was more often associated with CTD and infection, IDON was more likely to be associated with MS and NMO ($p=0.04$). OPN was bilateral in 26 (78.79%) patients compared to 17 (27.87%) patients with ($p<0.001$). Visual impairment in OPN was also less severe compared to IDON, as LogMAR visual acuity scores of patients with OPN 0.55 \pm 0.91 in OPN patients versus 1.19 \pm 1.24 in IDON patients ($p<0.001$). 11 (33.33%) OPN patients had ptosis in addition to 9 (27.27%) with diplopia and 10 (30.30%) with exophthalmos yet none of the IDON patients had these ophthalmologic findings.

4. OPN and rheumatic CTD

Graves' disease, IgG-4, and GPA were the major causes of OPN. Common clinical symptoms of OPN are ocular pain, decreased vision, and visual field defects and orbital MRI with abnormal enhancement around the optic nerve sheath (Table 3). However, OPN characteristics of patients with these rheumatic CTDs were different (Table 4). The most prominent feature of thyroid-associated ophthalmopathy (Graves' disease) was the thickening and protruding of extraocular muscles (Figure 3). Characteristic ophthalmologic findings in OPN patients with IgG-4 involved ocular herniation with involvement of trigeminal nerve branches, resulting in nerve thickening (Figure 4). In GPA patients, formation of an orbital inflammatory pseudotumor was found in the external space of the muscle cone, especially in the inner inferior quadrant (Figure 5). Soft tissue inflammation in the orbit was found in OPNs associated with CTDs along with otherwise abnormal contrast enhancement on the attachment point of the extraocular muscle (Figure 6). This suggests that inflammation of the soft tissue extending to optic nerve sheath may be part of the pathogenesis of OPN which could be due to increased vascular permeability, inflammatory cell leakage, and tissue edema.

Discussion

OPN is an uncommon orbit inflammatory disease (7) and most prior literature has come in the form of case reports (8). A cohort of 14 patients with idiopathic OPN was reported in 2001 (1). This study identified demographic and clinical characteristics of patients with OPN, which included mostly middle-aged females with unilateral presentation, +/- eye pain, mild visual impairment, and optic disc edema. Visual field abnormalities included arcuate defects, paracentral scotomas, central scotomas, and peripheral island defects (3). The clinical manifestations and characteristics of the patients in our study are quite different. This may be due to the differing OPN etiologies, as many of the patients in this small cohort had idiopathic OPN not associated with another specific condition.

It has been previously established that OPN is an orbital inflammatory disease that is different from IDON (9). Our study illustrates some of the differences between OPN and IDON, which include clinical characteristics, imaging features, and prognosis. We found that OPN are more often with CTD and IDON are more often associated with idiopathic inflammation, such as MS and NMO. Orbital MRI showed low or equal signal on T1WI and slightly low signal on T2WI. In OPN, contrast-enhanced scans showed that most of the optic nerve sheath presented a strip-like or nodular uniform enhancement with unclear boundaries.

Optic nerve and sheath enhancement were present in IDON. Soft tissue inflammation in the orbit has also been found in OPN, yet inflammation of the orbit is rare in IDON. Unlike OPN, optic nerve sheath enhancement in IDON is almost always accompanied by more prominent optic nerve parenchyma enhancement.

Known CTD etiologies of OPN include sarcoidosis (10, 11), GAP (12, 13), giant cell arteritis (14, 15), Crohn's disease (16), IgG-4 (17), Behcet's disease (9), and SLE (2). Infectious etiologies of OPN have been associated with acute retinal necrosis (18), syphilis (19, 20), herpes zoster (21), tuberculosis (22, 23), and *Mycoplasma pneumoniae* (24). In our study we found the primary causes of OPN were Graves' diseases (12), IgG-4(10), GPA (4), SLE (2), sarcoidosis (1), rheumatoid disease (1), scleroderma (1), Behcet's disease (1), gout (1), tuberculosis (5), sparganosis (1), ocular Toxoplasmosis (1), bacterial meningitis (1), fungal meningitis (1), and Cytomegalovirus (1). Unlike published reports, we did not find and OPN associated with syphilis and giant cell arteritis, which may be due to our small sample size and single center study. The finding of OPN associated with Graves' disease is unique to our study. We found that orbital fat inflammation was always associated with inflammation of the optic nerve sheath, suggesting that inflammatory invasion of orbital fat may be the primary pathogenic mechanism of OPN in patients with Graves' disease.

In GPA, formation of an orbital inflammatory pseudotumor was mainly concentrated in the external space of the muscle cone, especially in the inner inferior quadrant (25). OPN patients with IgG-4 often had ocular herniation involving the trigeminal nerve branches, which resulted in its thickening, suggesting perineural growth may be a characteristic imaging finding of OPN (26). The most prominent feature of thyroid-associated ophthalmopathy is the thickening and protruding of extraocular muscles (27). The trigeminal nerve branches were not involved in the OPN of the GPA patients in this study and the extraocular muscles were not thickened. We were unable to find any prior reports of trigeminal nerve branching and extraocular muscle involvement in patients with GPA, Graves', and sarcoidosis.

CTDs are a group of diseases that affect bones, joints, and surrounding soft tissue, such as muscles, bursa, tendons, fascia, and nerves (28). Chronic inflammation, mediated by T and B lymphocytes, eosinophils, and macrophages, activates fibroblasts to induce collagen deposition, and ultimately leads to tissue proliferation and dural thickening (29). The optic nerve is a continuation of the central nervous system with a dura, arachnoid, and pia mater. Therefore, the optic nerve sheath is also susceptible rheumatic CTDs. Orbital MRI showed low or equal signal on T1WI and slightly low signal on T2WI. Contrast-enhanced scanning showed that most of the optic nerve sheath had strip-like or nodular uniform enhancement with unclear boundaries. Most cases of soft tissue inflammation in the orbit have been found in OPN, differing it from the imaging findings in IDON. We speculate that OPN may be caused by orbital soft tissue inflammation and that the damage of the optic nerve sheath could be from antigen/antibody-mediated destruction associated with rheumatic disease.

Anti-myelin oligodendrocyte glycoprotein (MOG) autoantibodies have been identified in both children and adults with demyelination and are strongly associated with bilateral or recurrent optic neuritis (30). However, anti-MOG antibodies have not been found in patients with OPN (31) and we did not detect these antibodies in our study.

Limitations of this study include its retrospective design and recruitment of patients from only one medical center. Only 44 cases were included in this study due to inability to follow-up with some patients who initially met the inclusion criteria. Multi-center, large sample, case-control prospective studies are needed to further understand OPN pathogenesis and its relationship with other diseases.

Conclusions

OPN is often associated with CTDs such as Graves' disease, GPA, and IgG-4 disease. MRI findings of OPN patients included orbital fat inflammation, pachymeningitis, inflammation of optic sheath vessels, and edema of the optic nerve sheath which may provide insights into OPN pathogenesis. The possibility of OPN should be considered in the differential diagnosis of atypical optic neuritis to avoid misdiagnosis as IDON or other similar ophthalmologic pathologies discussed in this study.

Abbreviations

optic perineuritis
OPN
optica spectrum disorders
NMOSDs
multiple sclerosis
MS
optic neuritis
ON
magnetic resonance imaging
MRI
idiopathic demyelination optic neuritis
IDON
connective tissue disease
CTD
Immunoglobulin G4-related disease
IgG-4 RD
granulomatosis with polyangiitis
GAP

systemic lupus erythematosus
SLE
optic nerve sheath
ONS
Optical coherence tomography
OCT
Beijing Friendship Hospital
BFH
Anti-myelin oligodendrocyte glycoprotein
MOG

Declarations

Ethics approval and consent to participate

This study was approved by the BFH Ethics Committee and was conducted following the latest iteration of the Declaration of Helsinki (version:2019-P2-201-01). Participants were given written informed consent (version V1.1/2019-09-16) before inclusion in the study.

All of blood samples were collected as part of routine treatment for this study.

Consent for publication

Not applicable.

Availability of data and material

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

Competing interests

The authors declare that there is no conflict of interest regarding the publication of this article.

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Authors' contributions

L, HY and L, J was involved in the conception and design of the study. W, HH and W, ZC reviewed the orbit MRI images. S, J and L, J contributed to the acquisition, analysis and interpretation of data as well as drafting the manuscript and revising it critically. Z, H and W, YL were the duty of diagnosis the disease, L, J has also provided final approval of the version to be published. All authors have given final approval of the version to be published. All authors have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Tables

Table 1 OPN patient demographics and clinical characteristics

Number of patients (n)		44
Number of eyes associated with disease (n)		74
Median age, years (mean±SD)		52.64±17.42
Eyes with vision loss (n)		68
Eyes with papilledema (n)		55
Ptosis (n %)		11
Diplopia (n %)		9
Exophthalmos (n %)		10
Visual field defect		51
	Central scotoma n (%)	0(0%)
	Bjerrum Scotoma n (%)	0(0%)
	Ring Scotoma n (%)	27(52.94%)
	Irregular defect n (%)	16(31.37%)
	Diffuse visual field defect n (%)	8(15.69%)
Connective tissue disease		33
	Graves' disease	12
	IgG-4 RD	10
	GAP	4
	SLE	2
	Sarcoidosis	1
	Rheumatoid diseases	1
	Scleroderma	1
	Behcet's disease	1
	Gout	1
Infectious diseases		10
	Tuberculosis	5
	Sparganosis	1
	Ocular Toxoplasmosis	1
	Bacterial meningitis	1
	Fungal meningitis	1
	Cytomegalovirus	1
Idiopathic disease		1

GAP (Granulomatosis with Polyangiitis), SLE (systemic lupus erythematosus), IgG-4 RD (immunoglobulin G4-related disease)

Table 2 Clinical features of patients with OPN and CTDs versus IDON

	OPN with CTD	IDON	p
Number of patients (n)	33	61	
Number of eyes associated with disease (n)	59	78	
Sex ratio (M/F)	19/14	25/36	0.124
Median age, years (mean±SD)	54.21±17.10	44.56±14.59	0.004**
Bilateral involvement n (%)	26(78.79%)	17(27.87%)	0.000**
Acute onset n(%)	12(36.36%)	61(100%)	0.000**
Visual Acuity	LogMar score		
	0.55±0.91	1.19±1.24	0.000**
Ptosis, n (%)	11(33.33%)	0(0%)	0.000**#
Diplopia, n (%)	9(27.27%)	0(0%)	0.000**#
Exophthalmos, n (%)	10(30.30%)	0(0%)	0.000**#
Connective tissue disease n (%)	33(100%)	7(11.48%)	0.000**#
Anti-AQP-4- antibody	0 (0%)	7(11.48%)	0.040**
MS	0 (0%)	8(13.11%)	0.040#
NMOSD	0 (0%)	7(11.48%)	0.040#

MS (multiple sclerosis), NMOSD (neuromyelitis optica spectrum disorders) * = p <0.05, ** = p<0.01, # = Fisher's exact test

Table 3 Neuro-ophthalmic findings of OPNs with CTDs

Diseases	Cases (n)	Age (Year)	Sex (n, Male/Female)	Imaging	Ophthalmic involvement (n)	Unilateral or Bilateral involvement(n)	Treatment	Patients of Recurrence(n)
Graves' disease	12	32-77	7/5	Orbit MRI	Eye Pain: 5 10 Vision Loss: 11 Visual field defect: 11 Optic papilledema: 5	Unilateral: 3 Bilateral: 9	Glucocorticoid	3
IgG-4	10	39-80	7/3	Orbit MRI	Eye Pain: 7 7 Vision Loss: 9 Visual field defect: 9 Optic papilledema: 5	Unilateral: 1 Bilateral: 9	Glucocorticoid	2
GAP	4	23-72	3/1	Orbit MRI	Eye Pain: 3 4 Vision Loss: 3 Visual field defect: 3 Optic papilledema: 4	Unilateral: 1 Bilateral: 3	Glucocorticoid	2
SLE	2	29-58	0/2	Orbit MRI	Eye Pain: 0 Vision Loss: 2 Visual field defect: 1 Optic papilledema: 2	Bilateral: 2	Glucocorticoid	2
Sarcoidosis	1	60	0/1	Orbit MRI	Eye Pain: 1 Vision Loss: 1 Visual field defect: 1 Optic papilledema: 1	Bilateral: 1	Glucocorticoid	0
Rheumatoid disease	1	63	1/0	Orbit MRI	Eye Pain: 1 Vision Loss: 1 Visual field defect: 1 Optic papilledema: 1	Bilateral: 1	Glucocorticoid	1
Scleroderma	1	72	0/1	Orbit MRI	Eye Pain: 1 1 Vision Loss: 1 Visual field defect: 1 Optic papilledema: 1	Unilateral: 1	Glucocorticoid	1
Behcet's disease	1	15	0/1	Orbit MRI	Eye Pain: 1 Vision Loss: 1 Visual field defect: 1 Optic papilledema: 1	Unilateral: 1	Glucocorticoid	1
Gout	1	36	1/0	Orbit MRI	Eye Pain: 0 Vision Loss: 1 Visual field defect: 1 Optic papilledema: 1	Unilateral: 1	Glucocorticoid	1

Table 4 Orbital MRI findings of OPNs with CTD

Orbital MRI finding	Graves' disease (n=12)	IgG-4 (n=10)	GAP (n=4)	SLE (n=2)	Sarcoidosis (n=1)	Rheumatoid disease (n=1)	Scleroderma (n=1)	Behcet's disease (n=1)	Gout (n=1)
Abnormal contrast enhancement surrounding the intraorbital optic nerve	12	10	4	2	1	1	1	1	1
Orbit fat infiltration	12	10	4	2	1	1	1	1	1
Myositis	12	5	4	0	1	0	0	0	0
Trigeminal nerve branch involvement	0	9	0	0	0	0	0	0	0
Pterygopalatine fossa pseudotumor	0	0	4	0	0	0	0	0	0
Dacryoadenitis	10	10	4	0	1	0	0	0	0
Maxillary sinus disease	1	6	3	0	0	0	0	0	0
Paranasal sinus disease	1	7	4	0	1	0	0	0	0
Otitis mastoidea	0	0	3	0	0	0	0	0	0
Pachymeningitis	0	1	1	0	1	0	0	0	0

GAP (Granulomatosis with Polyangiitis), SLE (systemic lupus erythematosus), IgG-4 RD (immunoglobulin G4-related disease)

Figures

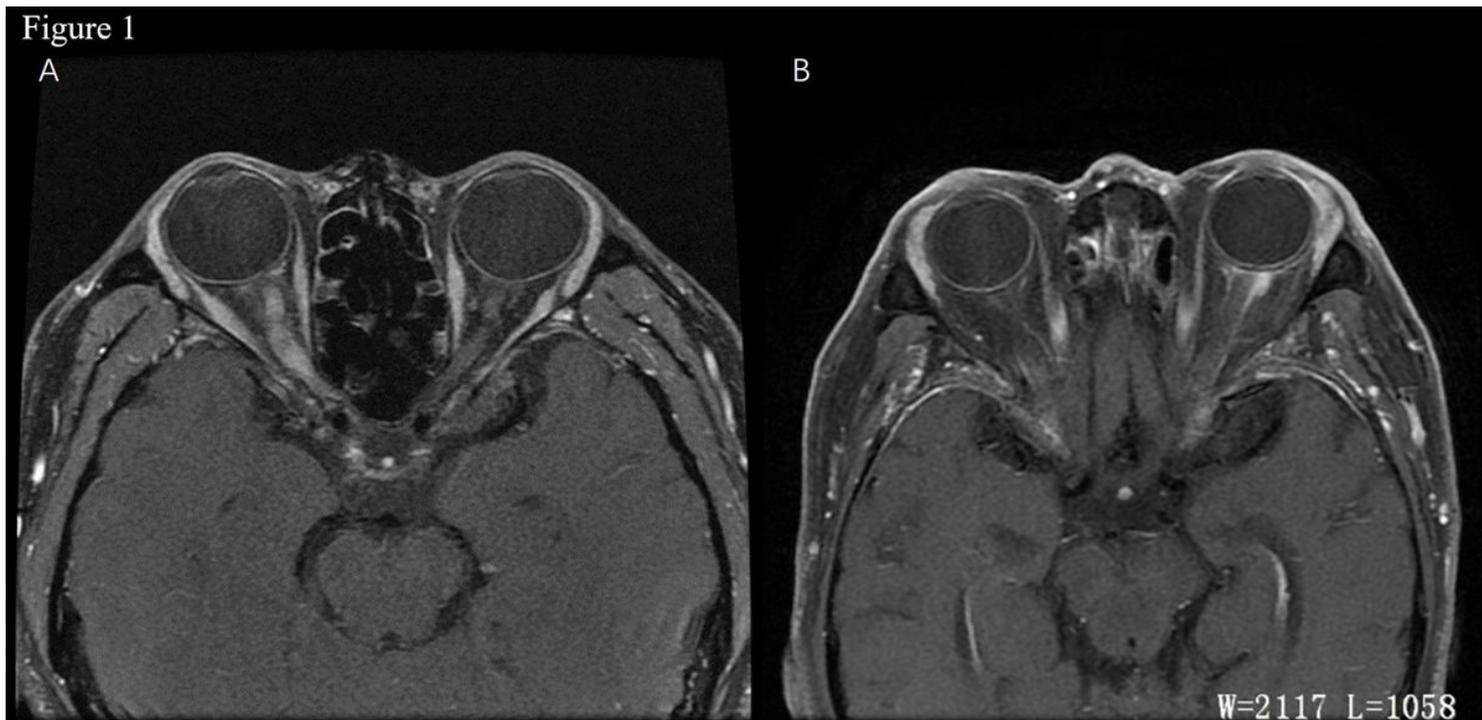


Figure 1
 Differences of ON and OPN in MRI A. ON: Axial T1 contrast image showed enhancement of right optic nerve B. OPN: Axial T1 contrast image showed enhancement of left optic sheath, not enhancement of optic nerve.

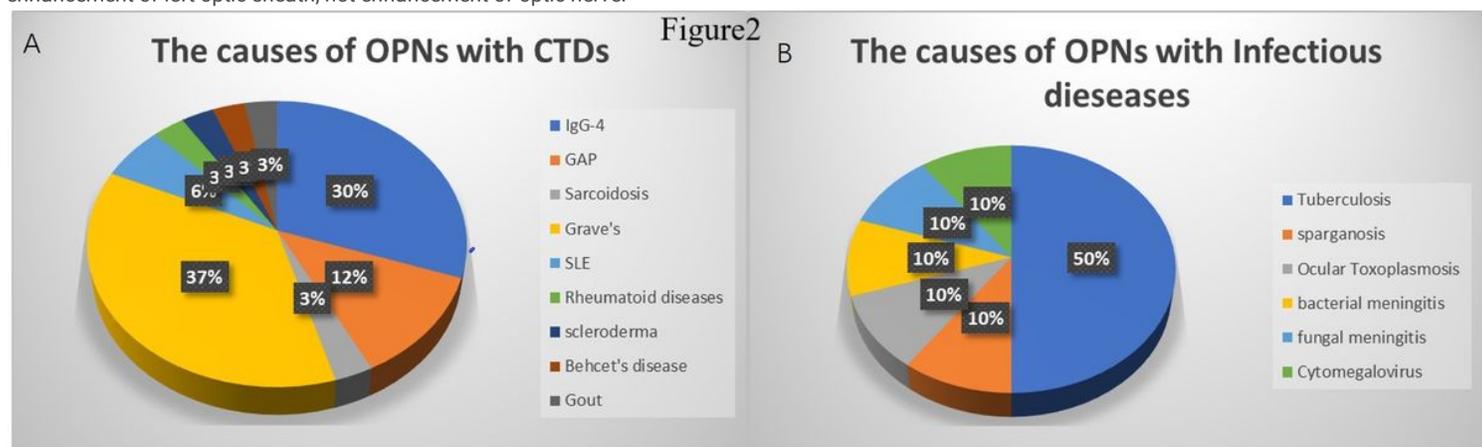
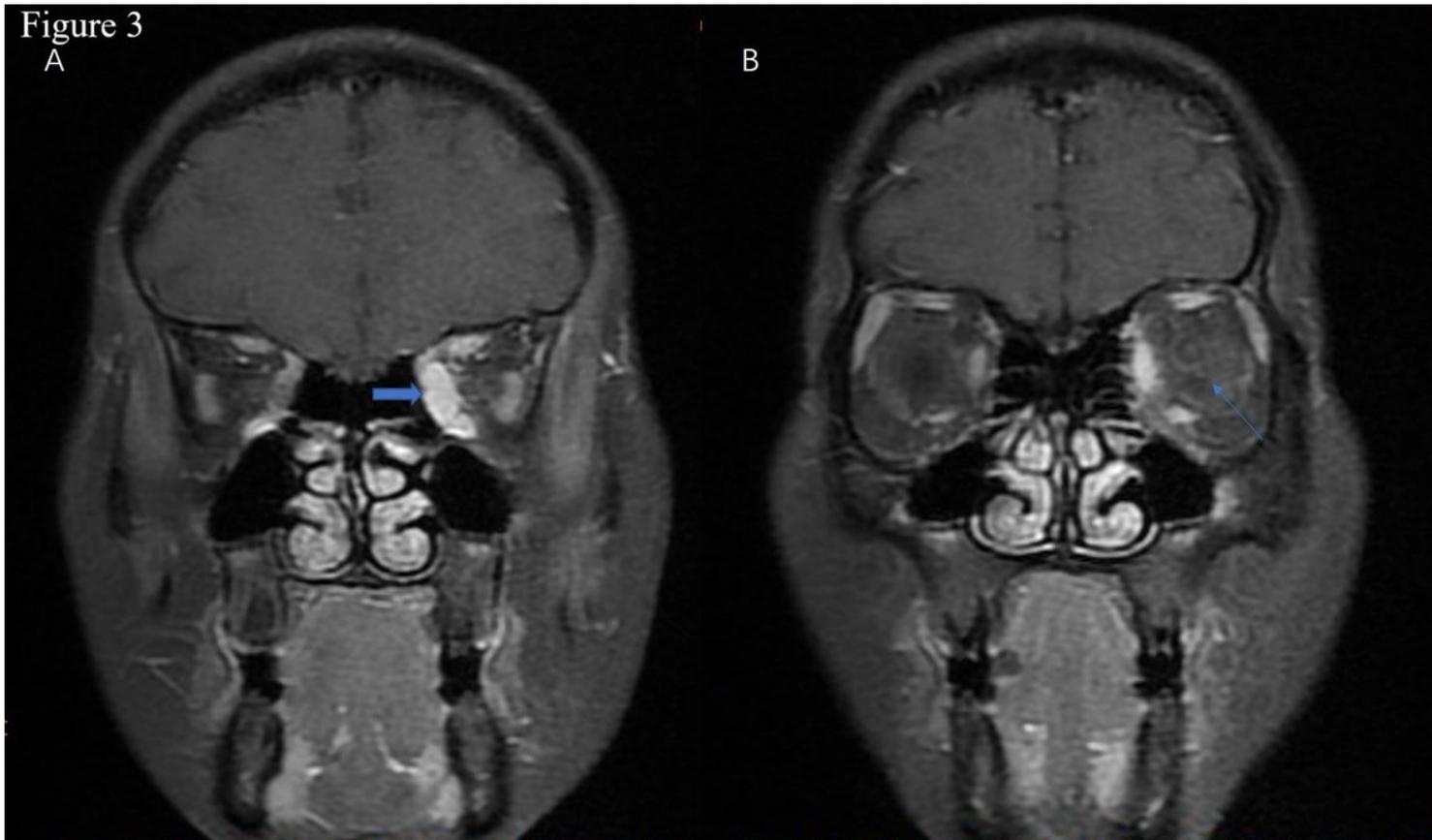


Figure 2
 OPN etiologies A. Connective tissue disease causes B. Infectious disease causes

Figure 3
A

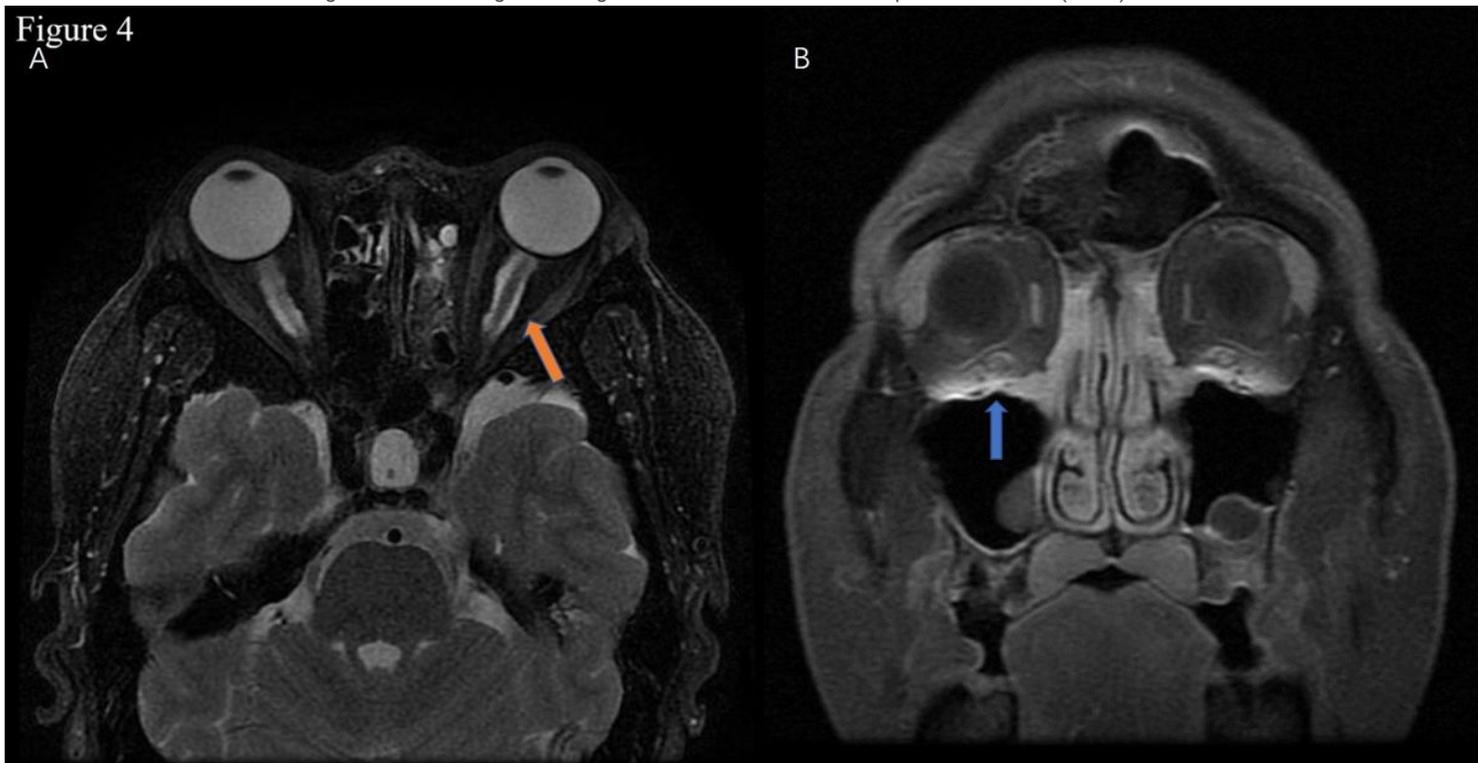


B

Figure 3

MRI findings of OPN patients with Graves' disease A. Coronal contrast enhanced T1-weighted MRI showing extraocular muscle belly enlargement (arrow) B. Coronal contrast enhanced T1-weighted MRI showing thickening and enhancement of the left optic nerve sheath (arrow).

Figure 4
A



B

Figure 4

MRI findings of OPN patients with IgG-4 RD A. Coronal T2-weighted MRI showing swelling and high signal of the bilateral optic nerve sheath (arrow). B. Coronal contrast enhanced T1-weighted MRI showing bilateral infraorbital nerve enlargement (arrow).

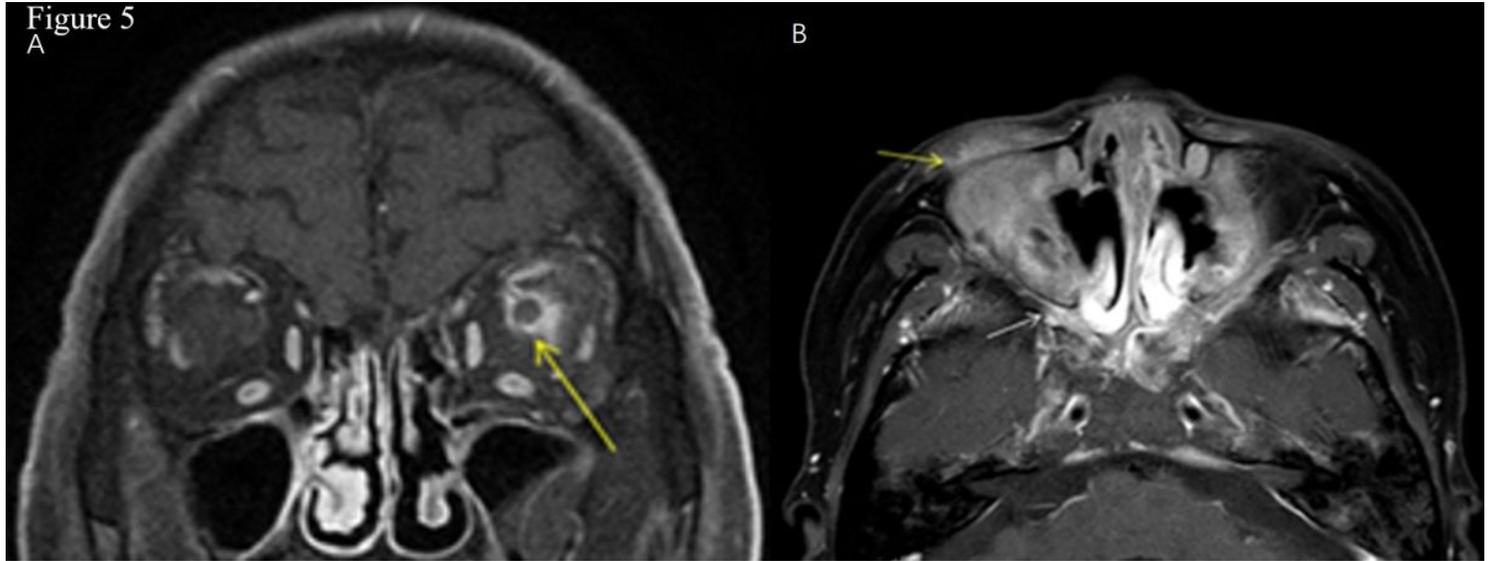


Figure 5

MRI findings of OPN patients with GAP A: Coronal contrast enhanced T1-weighted MRI showing thickening and enhancement of the left optic nerve sheath (arrow). B: Axial contrast enhanced T1-weighted MRI showing abnormal contrast enhancement shadow in the bilateral pterygopalatine fossa (white arrow) and inflammatory infiltration in the eyelid (yellow arrow)

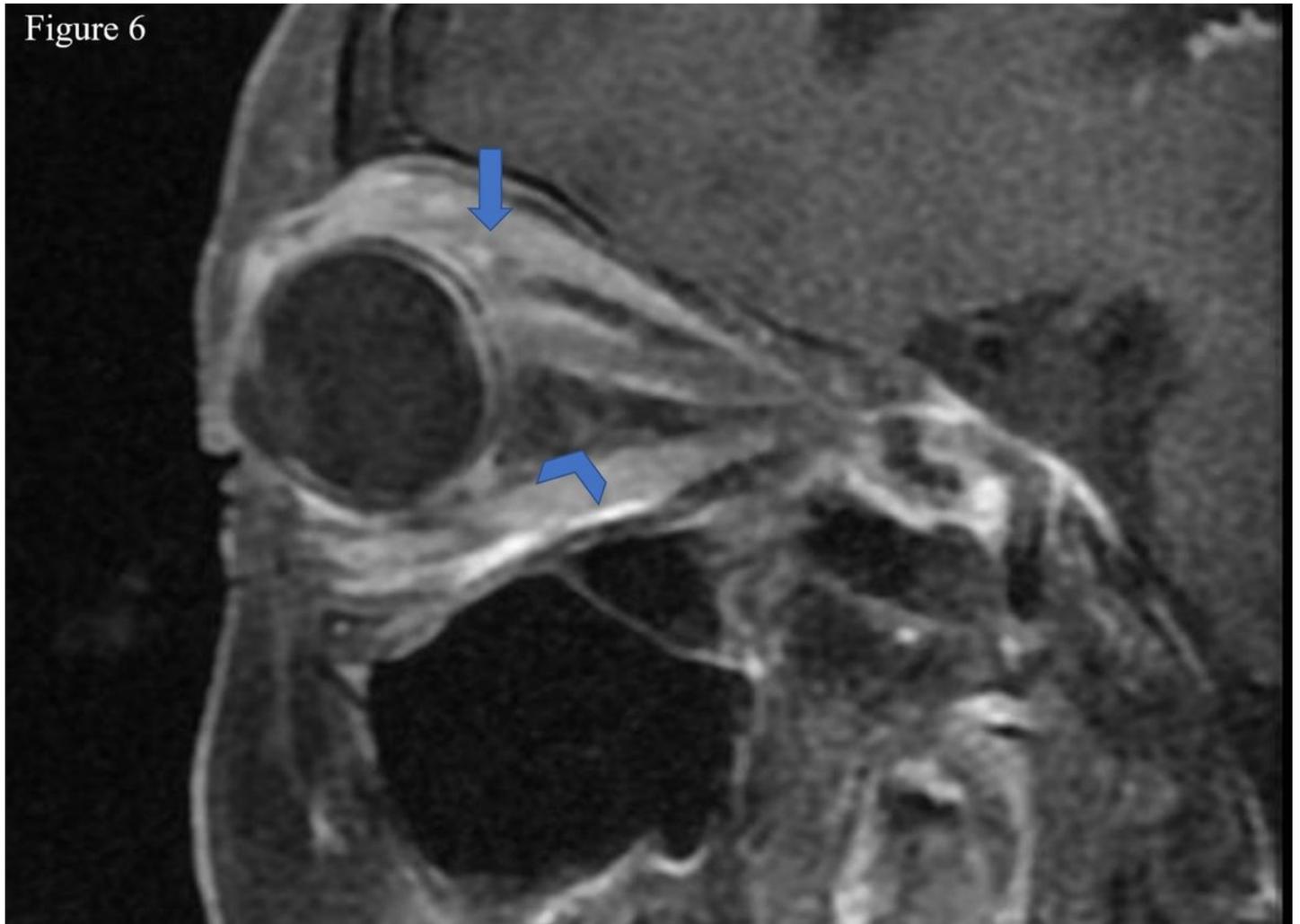


Figure 6

Orbital fat inflammation and inflammatory cell infiltration in OPN Sagittal contrast enhanced T1-weighted MRI showing orbit fat infiltration (arrowhead) and abnormal contrast enhancement on attachment point of the extraocular muscle (arrow)