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Enlargement of Multiple Branches of the Trigeminal Nerve in Non-Neoplastic Orbital Diseases: Review of MR Imaging in 14 Cases

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Keywords:

Perineural; Vasculitis; Trigeminal

Abbreviations:

IgG4-RD: IgG4 related disease; TGN: trigeminal nerve; RDD: Rosai Dorfman Disease; GPA: Granulomatosis with polyangiitis, or Wegener's disease; EGPA: Eosinophilic granulomatosis with polyangiitis, or Churg Strauss disease; PNS: perineural spread

1. Abstract

1.1. Background: Head and neck perineural disease is typically associated with cancer, but it can be associated with non-neoplastic conditions, especially IgG4-Related disease.

1.2. Purpose: We present the MRI findings of trigeminal nerve involvement in 14 patients with 3 different types of non-neoplastic orbital disease.

1.3. Material and Methods: A retrospective review of MR images of patients with enlargement of distinct TGN divisions who were evaluated in a neuro-ophthalmology clinic and were subsequently proved to have non-neoplastic orbital infiltrative or inflammatory diseases. Three experienced radiologists reviewed the MRI studies looking for extent and characteristics of perineural disease along the pathway of the 3 TGN divisions.

1.4. Results: MRI demonstrated enhancement of at least one TGN division in 14 patients with bilateral or unilateral orbital infiltrative non-neoplastic conditions (22 orbits). Six patients had IgG4-RD, 3 RDD, and 5 c-ANCA-associated vasculitis. Overall, 13 (92.8%) patients displayed enlargement of V2, 12 (85.7%) of V1 and 7 (50%) of V3. Simultaneous enlargement of V1 and V2 was detected in 11 (78.6%) patients, and all 3 divisions were simultaneously involved in 6 (42.8%). Other radiological findings included abnormal contrast enhancement and soft tissue thickening in the cavernous sinus, Meckel's cave, and/or the cisternal segment of the trigeminal nerve.

1.5. Conclusions: Although trigeminal thickening associated with non-malignant orbital infiltration is commonly considered a sign of IgG4-RD, other conditions such as vasculitis and RDD should be considered in the differential diagnosis of these uncommon cases.

2. Introduction

TGN enlargement is usually a sign of perineural spread of head and neck malignancies. TGN enlargement in non-neoplastic head and neck diseases occurs but is rare compared with perineural spread due to malignancies such as squamous cell carcinoma and adenoid cystic carcinoma]. There are only scattered case reports of trigeminal involvement in sinonasal sarcoidosis [1], rhinocerebral mucormycosis [2], nonspecific inflammatory conditions [3, 4], amyloidosis [5], and granulomatosis with polyangiitis (Wegener disease) involving the pterygopalatine fossa [6] and cavernous sinuses [7, 8].

In 2011 Katsura et al. reported a patient with isolated enlargement

of V2 and V3 branches due to an inflammatory process diagnosed as IgG4-RD [9]. Following this report, TGN enlargement, especially of the infraorbital nerve, has been strongly associated with IgG4-RD [10-18], Widespread involvement of the TGN is an important feature of IgG4-related disease [19] and less frequently with idiopathic inflammation [20] and lymphoid hyperplasia [16]. Herein we present a new finding of group of patients with orbital disease in whom different TGN divisions were enlarged not only with IgG4-RD, but also with vasculitis and RDD with bilateral perineural enhancement even in unilateral eye disease.

3. Material and Methods

This is an institutional review board-approved retrospective analysis of medical records of patients who presented for assessment of non-malignant orbital lesions and MRI evidence of trigeminal perineural disease. Only patients with a biopsy-proven diagnosis of their orbital diseases and MRI imaging of the orbits and head and neck showing evidence of perineural trigeminal disease were included. Diagnoses were based on the histopathologic characteristics of the tissue samples as well as on the results of immunohistochemical staining for IgG, IgG4, CD 20, CD 3, CD68, S100, and CD1A.

3.1. Imaging Technique

Patients underwent imaging either with a Philips Achieva 3T machine (Philips Healthcare, Best, the Netherlands) with a 16 or 32-channel Philips head array coil, or with a 3-T scanner (Magnetom Allegra; Siemens, Erlangen, Germany) with a dedicated 32-channel head coil. The imaging protocol included T1- and fat saturation T2-weighted sequences on the sagittal, axial and coronal planes of 3 mm-thick sections and no interslice gap. Post-contrast T1-weighted fat-suppressed images (Magnevist; Schering, Berlin, Germany,TR/TE = 400–575/13–15 ms) were also obtained for all patients. Additional acquisition included high resolution three-dimensional constructive interference in steady state sequences (CISS sequence, repetition time 10.76 ms, echo time 5.38 ms, 70° flip angle, 200 × 200 mm field of view, 512 × 512 mm matrix, and 64 slices

The radiological studies of the patients were reviewed by three experienced neuroradiologists blinded to patient history, symptoms, and histopathologic data, using a digital imaging and communications in Medicine (DICOM) viewer system (Horos, https://horosproject.org/) and Enterprise Imaging Agfa HealthCare. The diagnosis of trigeminal perineural disease was based on the classical findings of nerve enlargement or enhancement, obliteration of the fat planes around the nerves and their foramina, and enlargement and/or erosion of foramina, canals and fissures [19-21].

Perineural disease was characterized according to which right- or left-sided branch of V1, V2 and/or V3 was affected. Pertinent intracranial and extracranial structures (cavernous sinus, Meckel's cave, superior orbital fissure, pterygopalatine fossa, foramen rotundum, foramen ovale, vidian and pterygoid canals) and cisternal segment of TGN were also carefully assessed.

4. Results

Fourteen patients with three different etiologies of orbital disease and TGN enlargement were identified. No patient had any complaints associated with trigeminal dysfunction such as hypo- or hyperesthesia. Patients' demographic data, diagnosis, laterality, type of orbital involvement and clinical findings are summarized in Table 1.

IgG4-RD was present in 6 patients. Orbital biopsies revealed the typical lymphoplasmacytic infiltrate with significant plasma cell positivity for IgG4 (IgG4+/ IgG ratio ≥ 40%). The infraorbital nerve of patient # 13 was also biopsied.

Vasculitis associated with c-ANCA (cytoplasmic antineutrophil cytoplasmic antibodies) positivity was diagnosed in 5 patients, three patients with GPA and 2 with EGPA. Orbital tissue samples from these patients showed granulomatous necrotizing vasculitis, with a significant eosinophilic infiltrate in the two EGPA cases.

RDD was diagnosed in 3 patients whose orbital biopsies showed sheets of histiocytes with the characteristic emperipolesis admixed with lymphocytes and plasma cells. The histiocytes stained positive for CD68 and S100 and negative for CD1A. One patient also displayed a significant ratio of plasmocytes positive for IgG4 (IgG4+/IgG = 85%). A biopsy of the supraorbital nerve of patient # 7 was also obtained.

The distribution of the divisions with at least one nerve enlarged is shown in Table 2. Table 3 lists the enlargement of different nerves by patient and disease. TGN involvement was not restricted to a single TGN division in any patient. Although V2 was the most affected in all groups, at least one nerve of V1 or V3 was bilaterally enlarged in all groups, including the patients with unilateral orbital disease.

It is important to highlight the frequent enlargement of the frontal nerve in IgG4-RD because the involvement of this branch is rarely mentioned in the majority of articles about this condition. Another interesting finding is the extension of V2 enlargement into the PPF seen in all groups. The Vidian nerve, which is not a part of the TGN, was also commonly affected. Although less frequent, perineural disease in V3 nerves was present in the various groups of diseases.

Figures 1 to 4 illustrate representative cases. RDD patient whose MRI is shown in Figure 1, developed massive orbital infiltration and multiple dural lesions similar to meningiomas with enlargement of all main branches of V2 and V3 despite immunosuppressive therapy. Figure 2 shows a patient with IgG4-RD with massive Infraorbital Nerve (ION) enlargement and bilateral involvement of V3 branches.

The patient shown in Figure 3 was a known case of EGPA with a positive history of sinusitis, asthma, pulmonary ground glass

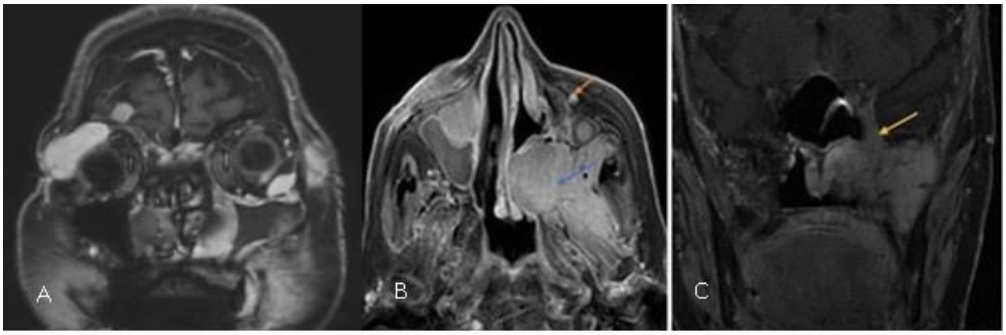
opacities, eosinophilia, and an orbital biopsy that revealed a polyclonal lymphoplasmacytic infiltrate with giant cells, vasculopathy and eosinophils. He had undergone a bilateral 3-wall decompression to control his disfiguring proptosis and had been treated with cyclophosphamide and methotrexate. A case of GPA is shown in Figure 4.

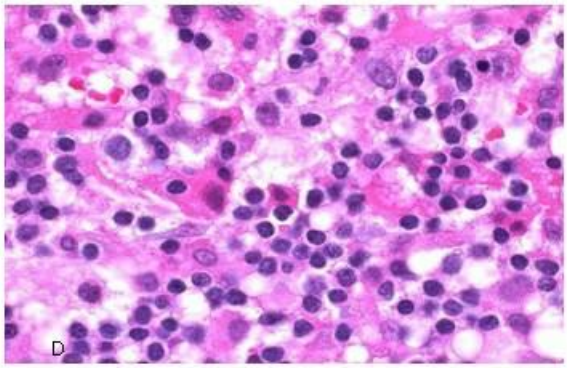
Table 1: Diagnoses, orbital involvement and clinical findings

Case	Sex	Age (yrs)	Diagnosis	Laterality	Orbital involvement	Clinical findings				
						Proptosis	Eye motility limitation	Chemosis	Conjunctival hyperemia	Optic neuropathy
1	F	37	IgG4 RD	Bilateral	Lacrimal gland, extraocular muscles, apex	Y	Y	N	N	Y
5	F	49	IgG4-RD	Bilateral	Lacrimal gland, apex	Y	N	N	N	Y
9	M	60	IgG4 RD	Bilateral	Lacrimal gland	Y	N	N	N	N
10	M	66	IgG4 RD	Bilateral	Intraconal mass	Y	N	Y	Y	Y
12	F	52	IgG4 RD	Right	Lacrimal gland	N	N	N	N	N
13	M	72	IgG4 RD	Right	EOM, intraconal mass	Y	N	Y	Y	N
3	M	28	EGPA	Right	Diffuse	Y	Y	N	Y	N
4	M	25	EGPA	Bilateral	Diffuse	Y	Y	N	Y	Y
8	F	33	GPA	Bilateral	Diffuse	Y	N	Y	Y	N
11	F	78	GPA	Left	Diffuse	Y	N	N	N	N
14	M	85	GPA	Right	Inferior oblique muscle, inferior and medial recti	Y	N	N	Y	N
6	F	77	RDD/ IgG4+	Right	Inferior rectus muscle	Y	Y	N	Y	N
7	M	39	RDD	Bilateral	Bilateral inferior rectus muscle, left medial rectus , bilateral lacrimal gland	Y	Y	N	N	N
2	F	72	RDD	Bilateral	Right lacrimal gland, left inferolateral mass	N	N	N	N	N

Table 2: Number (%) of patients with enlargement of TGN divisions

Disease	Trigeminal enlargement				
	V1	V2	V3	V1+V2	V1+V2+V3
IgG4 -RD	5 (83.3)	6 (100.0)	3 (50.0)	5 (83.3)	3 (50.0)
Vasculitides	4 (80.0)	4 (80.0)	2 (40.0)	3 (60.0)	1 (20.0)
RDD	3 (100.0)	3 (100.0)	2 (66.7)	3 (100.0)	2 (66.7)
All	12 (85.7)	13 (92.8)	7 (50)	11 (78.6)	6 (42.8)





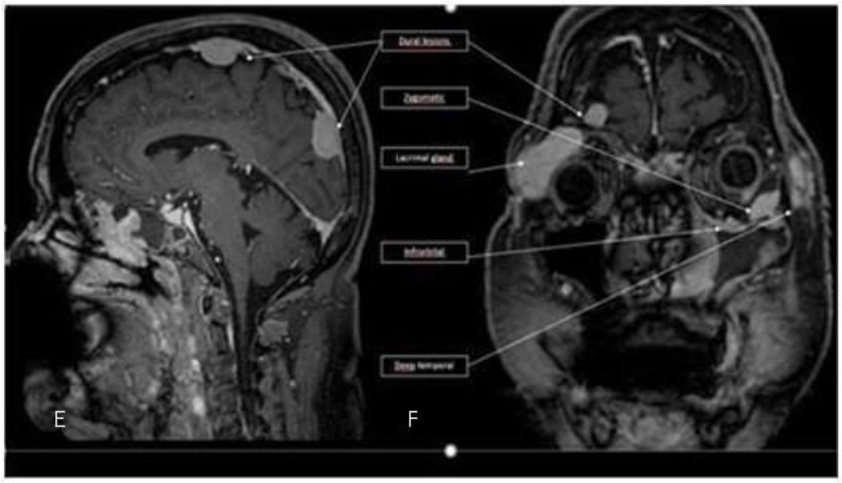


Figure 1: A-C**:** coronal, axial and sagittal T1 fat sat post contrast Images showed extensive involvement of both orbits, lacrimal glands, left masticator space mass (blue arrow),extension through the oval foramen (yellow arrow) in the left Meckel'scave(green arrow) Enhancement along left infraorbital nerve(orange arrow) with infraorbital and zygomatic nerve enhancement. D: The histopathological appearance of lymphocytic and histiocytic infiltrate in a patient with RDD with typical emperipolesis (original magnification × 1000, Hematoxylin & eosin). Follow up MRI E,F: Despite medical treatment, the patient developed multiple dural based lesions and massive orbital infiltration with enlargement of all main branches of V2 and V3.

Table 3: Distribution of nerve enlargement by TGN division, patients and disease

Disease	Patient	Orbital Involvement	V1						V2										V3							
			FR		NC		LC		IO		ZYG		GP		LP		SA		AT		DT		IA		BC	
			R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L
IgG4-RD	1	Bilateral	+	+	-	-	-	-	+	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-
	9	Bilateral	+	+	-	-	+	+	+	+	-	-	+	+	+	+	+	+	-	-	-	-	-	-	-	-
	10	Bilateral	+	+	-	+	-	-	+	+	-	+	-	+	-	+	+	+	-	-	-	-	-	-	-	-
	12	Right	+	+	-	-	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	-	+	+	+	+
	13	Right	+	-	-	-	-	-	+	+	+	-	+	-	+	-	-	-	-	-	+	+	+	+	+	+
	5	Bilateral	-	-	-	-	-	-	+	+	-	-	+	+	+	+	+	+	-	-	-	-	+	+	-	-
Churg-Strauss	3	Bilateral	-	-	-	-	-	-	+	+	-	-	+	+	+	+	+	+	-	-	-	-	+	+	-	-
	4	Bilateral	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	-	-	-	-	+	+	+	+
Wegener	8	Bilateral	-	-	-	+	+	+	+	+	+	+	-	-	-	-	+	+	-	-	-	-	-	-	-	-
	11	Left	-	-	-	+	-	+	+	+	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	14	Right	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Rosai-Dorfman	2	Bilateral	-	-	-	-	+	+	-	+	+	+	-	+	+	+	+	+	+	+	-	+	-	-	-	-
	6	Right	-	+	-	-	-	-	+	+	-	+	+	+	-	+	-	+	-	-	-	-	-	-	+	+
	7	Bilateral	+	+	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Nerves: Fr = frontal, NC = Nasociliar, LC = lacrimal, IO = infraorbital, Zyg = zygomatic, GP = greater palatine, LP = lesser palatine, SA = superior alveolar, AT = anterior temporal, DT = Deep temporal, IA = Inferior alveolar, BC = Bucal, VD = Vidian.

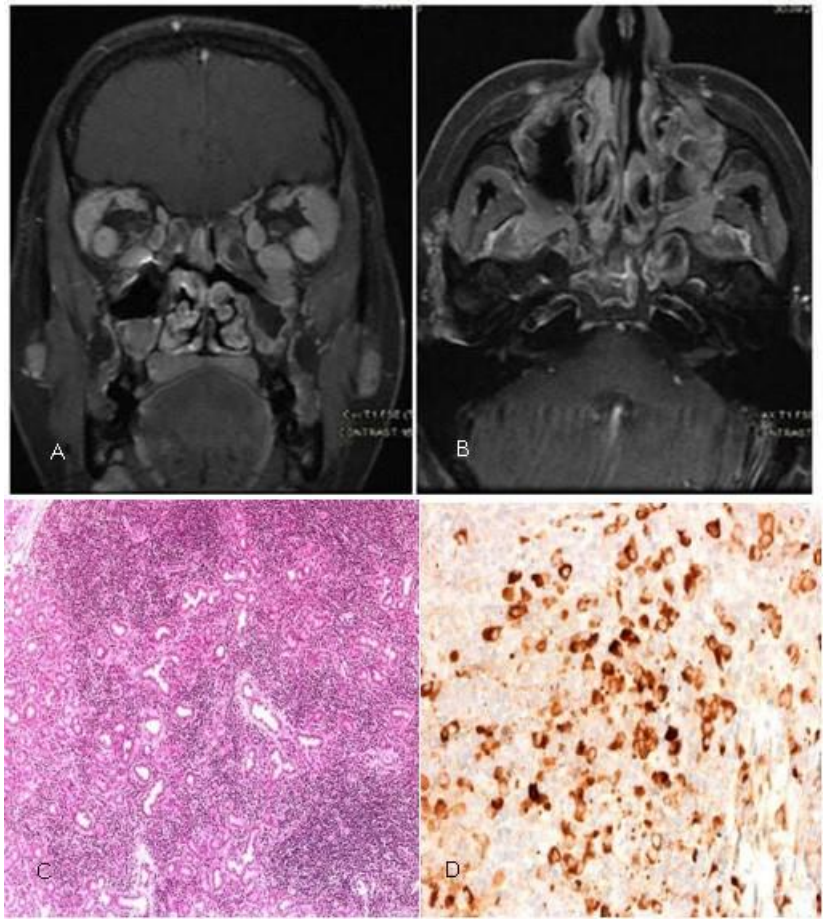


Figure 2 : IgG4-related disease: A&B: coronal and axial post contrast fat suppressed images showed enlargement of extraocular muscles, lacrimal gland, and divisions of the trigeminal nerve. C: Biopsy from lacrimal gland and the left infraorbital canal demonstrated lymphoplasmacytic infiltrate and fibrosis (Original magnification x 100 Hematoxylin & eosin). D: Histopathological image of numerous plasma cells expressing reactivity to IgG4 marker (Original magnification x 400 IgG4 stain).

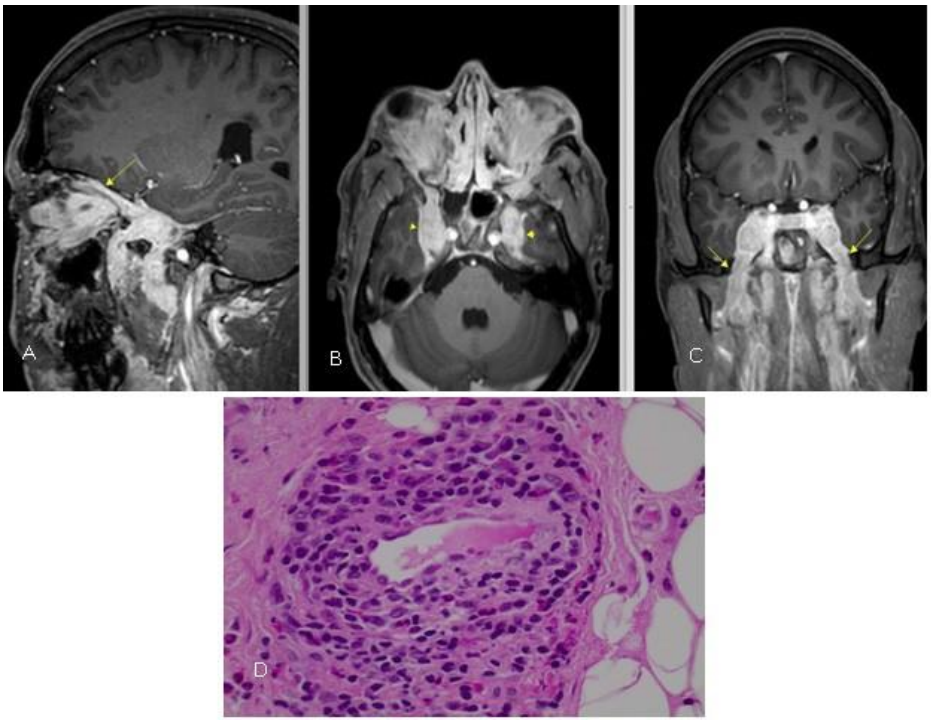


Figure 3: Eosinophilic Granulomatosis with polyangiitis (Churg Strauss syndrome). A-C extensive involvement of both orbits, bilateral cavernous sinuses, Meckel cavum, foramen rotundum ,palatine nerves and PPF involvement. D: Higher magnification of the vasculitis affecting the orbital small blood vessels, which shows polyclonal lymphocytes and numerous eosinophils surrounding the blood vessels (Original magnification x400, Hematoxylin & eosin).

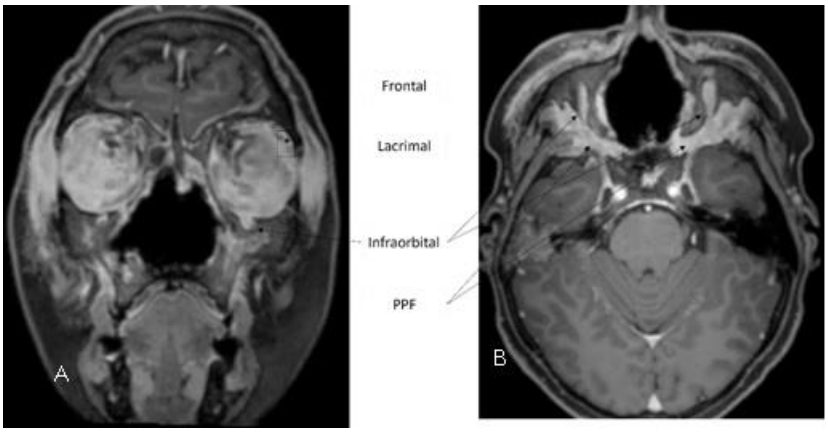


Figure 4: Granulomatosis with polyangiitis, or Wegener's disease A&B: coronal and axial post contrast fat suppressed images showed extensive orbital involvement PPF and vidian nerve involvement, and IO nerve thickening.

5. Discussion

Our data indicate that involvement of the TGN in different types of infiltrative non-neoplastic orbital diseases is a widespread phenomenon involving V1, V2 and V3, Meckel's cave, cavernous sinus and pterygopalatine fossa.

The literature on this subject is limited and mainly centered on IgG4-RD. In 2011, two articles from Japan associated infraorbital nerve (ION) enlargement with IgG4-RD. Watanabe et al. were the first to show that ION enlargement was frequently observed in patients with autoimmune pancreatitis [24], and Katsura et al. reported a patient with a mass containing abundant IgG4 + plasma cells involving the ION, PPF and Meckel cave. The ipsilateral foramen ovale was expanded without signs of bone destruction [9]. One year later, Inoue et al. described lesions involving the infraorbital and supraorbital nerves in 5 patients with IgG4-RD [11]. Following these early reports, several articles have stressed the association between IgG4-related orbital disease and ION enlargement [10, 13, 15-17, 25-28]. We believe that the emphasis on ION enlargement may simply be related to the proximity of these branches to the orbital contents. The nerve is easily assessed In both CT and MRI coronal and axial slices, and it is a natural part of the orbital imaging search pattern, while involvement of other TGN branches is visualized only if a thorough TGN interrogation is undertaken [29]. In our patients, not only were other V2 branches affected, but also 75% of the supraorbital nerves were also involved. If the entire course of the TGN is carefully studied, V1 and/or V3 branches may be found to be abnormally enlarged.

The present case series demonstrates that enlargement of the TGN is not a specific sign. Both the vasculitides GPA and EGPA may show a pattern of TGN involvement similar to that of IgG4-RD. This finding is surprising because we were not able to find any report in the literature similar to our data. Pure sensory neuropathy is not common in ANCA-associated vasculopathy and, when it happens [30], the neural disease is considered to be caused by an ischemic occlusion of the vasa nervorum. The axons are affected, inducing symptoms such as pain and dysesthesia [6, 30]. Our patients did not report any signs or symptoms related to TGN infiltration and enlargement. This absence of symptomatology concurs well with previous observations that TGN enlargement rarely causes neurological symptoms in IgG4-RD [11].

Trigeminal involvement in RDD has not been reported in earlier reviews. A literature review of 210 cases of RDD of the central nervous system did not mention this type of lesion [31]. Most cases of intracranial RDD exhibit dural-based lesions mimicking meningiomas, as observed in our patient # 2 [32]. Since the coexistence of perineural disease and dural lesions is highly suggestive of neoplastic disease, it is important to recognize that this pattern can be found in RDD and thus avoid unnecessarily aggressive surgical excision of intracranial masses.

Perineural infiltration in RDD is also interesting because it has been demonstrated that plasma cells expressing IgG4 are found in a subset of extranodal RDD [33, 34]. Patient #7 of the present series presented with an orbital lesion with abundant IgG4+ plasma cells associated with TGN enlargement. There is a previous report of an orbital case of RDD associated with IgG4 which, unfortunately, was not imaged [35]. As our 2 other RDD cases did not show features of IgG4, we cannot support any causal relationship between TGN enlargement and the presence of IgG4+ plasma cells in RDD.

Although the term "perineural spread" has been used to describe inflammatory and non-neoplastic enlargement of the TGN [36], it is questionable whether this terminology is appropriate to describe these changes. PNS means that specific cells, usually malignant, have left the site of the primary lesion and are travelling along a nerve. PNS is thus a form of a metastatic disease where the tumor can disseminate along the endoneurium or perineurium to distant areas of the body [37]. The pattern of distribution of TGN enlargement associated with orbital inflammatory/infiltrative disease does not support this concept. All patients with unilateral orbital infiltration showed at least one branch enlarged on the side contralateral to the affected orbit. Our case series supports that TGN enlargement associated with inflammatory orbital conditions is a component of the systemic disease that affects simultaneously the orbit and the TGN and not a disease that is spreading in a primarily contiguous fashion through the TGN.

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