

# Clinical Reasoning: A 51-Year-Old Woman With Diplopia and Headache

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## Abstract

A 51-year-old woman presented with a pressure-like headache behind her right eye and horizontal diplopia. On examination, she was unable to abduct or adduct the right eye but had intact vertical eye movements. Her deficits could not be overcome using the oculoccephalic reflex. Imaging initially was interpreted as optic neuritis, but on careful review with radiology, a diffuse enhancing hyperintense signal within the orbital apex confirmed an orbital infiltrate. The focus of this case study is to review the localization approach for diplopia and build a differential diagnosis for orbital processes. Another key point is the importance of relying on the physical examination as the guide to a patient's management rather than imaging findings, which can often be misleading.

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## Glossary

APD = afferent pupillary defect; IgG = immunoglobulin G; IgG4-RD = IgG-4-related disease.

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### Section 1

A 51-year-old right-handed woman presented to the hospital with a 3-day history of nonradiating, pressure-like headache behind her right eye. By the third day, she noted diplopia. She denied any scalp tenderness, fever, weight loss, malaise, or fatigue. She recalled having similar pressure behind the eye a few years ago, which was attributed to sinus disease and had resolved with steroids. She had no past medical problems and is not on medications.

On examination, she had unremarkable vital signs and was fully alert and oriented with intact language. Confrontation visual fields were normal in both eyes. She endorsed

horizontal diplopia that resolved when covering either eye. She was unable to abduct or adduct the right eye but had intact vertical eye movements in the right eye. Oculocephalic testing was abnormal in the right eye with horizontal head movement. Extraocular movements were fully intact in the left eye. Pupils were equally round and reactive to light without anisocoria or afferent pupillary defect (APD), and the eyelids were symmetric. The rest of her cranial nerves were intact as well as her motor, sensory, coordination, and reflex testing. In the emergency department, she underwent CT of the head, which was normal.

#### Question for Consideration:

1. How do you classify and localize diplopia?

**GO TO SECTION 2**

## Section 2

When approaching diplopia, the first step is to differentiate a monocular from binocular diplopia (eAppendix 1, [links.lww.com/WNL/C246](https://links.lww.com/WNL/C246)). The patient had horizontal binocular diplopia with significant restriction in extraocular movement in the horizontal plane. CN VI (nuclear/nerve) can account for the impairment in abduction. CN III cannot be globally involved because her vertical gaze, pupils, and eyelid strength were intact. Her presentation is inconsistent with an internuclear ophthalmoplegia, which would present as slowed adduction ipsilaterally and contralateral abduction nystagmus. Supranuclear palsy is also unlikely in the absence of other brainstem or cerebellar signs, and her deficit cannot be overcome using the oculocephalic reflex (doll's eyes).

Neuromuscular junction disorders and infiltrative muscular/orbital lesions should be considered in the differential because they can present with similar vision complaints and examination findings.

The patient underwent MRI of the brain and orbits, which was interpreted by radiology as asymmetric abnormal enhancement and increased T2 signal intensity within the intracanalicular and proximal intraorbital segments of the right optic nerve sheath complex, consistent with right-sided optic neuritis.

### Questions for Consideration:

1. Does the MRI finding change your localization?
2. How would you like to proceed?

**GO TO SECTION 3**

### Section 3

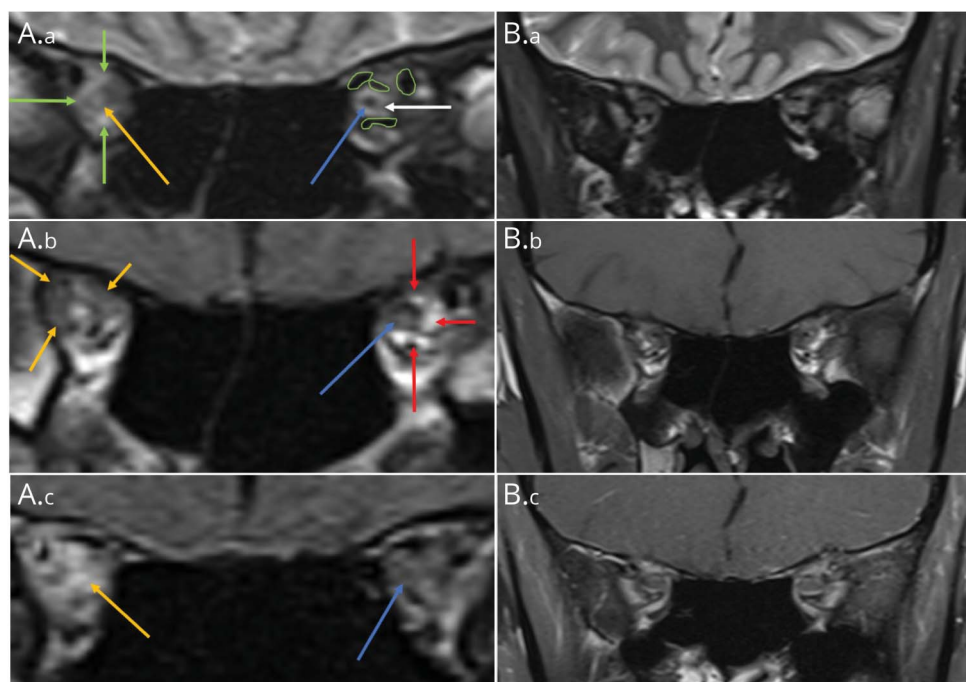
The MRI finding of optic neuritis is a bit perplexing because the patient's presentation did not suggest an afferent visual disorder but rather an efferent one. Optic neuropathies typically involve loss of visual acuity, color, visual field deficits, and often an APD (in unilateral vision loss). Although the optic nerve may appear normal in retro-orbital pathologies, atrophy should be noted once loss is chronic. Given this inconsistent finding, a neuro-ophthalmology consult was obtained. The examination revealed a normal afferent visual function; however, as noted earlier, she was not able to abduct or adduct the right eye. The remainder of

her efferent examination was unremarkable. Because her neuro-ophthalmologic examination did not reveal an optic neuropathy, a careful review of the images was performed with radiology (Figure 1, A.a–A.c), revealing a diffuse enhancing hyperintense signal within the orbital apex with loss of the normal anatomic detail, in addition to the hyperintensity within the optic nerve, confirming an orbital process as the likely source for her pathology.

#### Questions for Consideration:

1. What is your differential diagnosis?
2. What additional tests would you like to order?

**Figure 1** Right Orbital Apex Infiltrate on MRI



(A.a) Coronal STIR sequence: the normal left orbital apex shows a normal relatively hypointense signal of the left optic nerve (blue arrow), surrounded by normal hyperintense CSF (white arrow), which in turn is surrounded by the thin hypointense optic nerve sheath. The small peripheral hypointense linear structures (outlined in green) in the orbital apex are the origins of the partly imaged extraocular muscles. In comparison, the abnormal right orbital apex shows a diffuse hyperintense STIR signal (green arrows), with loss of the normal anatomic detail. In addition, the right optic nerve shows a central region of hyperintense STIR signal (yellow arrow). (A.b) Coronal T1 precontrast image: The normal left orbital apex shows a normal relatively hypointense signal of the left optic nerve (blue arrow) and surrounding CSF, which in turn is surrounded by normal T1 hyperintense orbital apical fat (red arrows). The abnormal right orbital apex shows abnormal T1 hypointense signal (yellow arrows) with loss of the expected hyperintense signal of T1 orbital fat and loss of identification of the right optic nerve (because of the similar T1 signal of the optic nerve and the abnormal surrounding soft tissue in the right orbital apex). (A.c) Coronal T1 postcontrast image: The left (blue arrow) orbital apical fat (as well as normal fat in all other anatomic sites on this image) loses its T1 hyperintense signal. The right orbital apex has marked abnormal enhancement of nearly the entire apex (yellow arrow). (B.a) Coronal STIR sequence: There is resolution of abnormal right orbital apex and optic nerve hyperintense STIR signal. The orbital apices are now symmetric and normal. (B.b) Coronal T1 precontrast image: Sharp anatomic detail of the right orbital apex is restored. (B.c) Coronal T1 postcontrast with fat suppression image: There is complete resolution of abnormal enhancement of the right orbital apex and optic nerve. The orbital apices now are symmetric and normal.

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## Section 4

The differential diagnosis for intraorbital pathologies includes tumors (lymphoma, optic nerve glioma, optic nerve sheath meningioma, and metastasis), vascular (cavernous hemangioma, orbital venous varix, arteriovenous malformation, and lymphangioma), inflammatory/infiltrative (orbital pseudotumor, orbital sarcoidosis, thyroid orbitopathy, immunoglobulin G [IgG]-4-related sclerosing disease, histiocytosis, and granulomatosis with polyangiitis), and infectious etiologies (orbital tuberculosis and orbital cysticercosis).

Laboratory workup included a complete blood count, comprehensive metabolic panel, thyroid function tests, and acetyl

choline receptor antibodies, all of which were negative. Her erythrocyte sedimentation rate and C-reactive protein were both elevated at 141 (normal 0–30 mm/hr) and 1.94 (normal <0.30 mg/dL), respectively. Serum testing for autoimmune conditions was negative. The total IgG level was 2,810 (normal 700–1,600 mg/dL). CSF testing revealed normal cell count, protein, glucose, and angiotensin-converting enzyme. No oligoclonal bands were noted. Chest CT did not reveal any mediastinal or hilar adenopathy. Brain MRA was normal without evidence of vascular malformations.

### Questions for Consideration:

1. What is the diagnosis?
2. How would you manage the patient at this time?

GO TO SECTION 5

## Section 5

The elevation of inflammatory markers and MRI findings suggest an inflammatory infiltrate within the orbit such as orbital pseudotumor. The elevation of IgG suggests IgG-4-related disease, although the subclasses had not yet been analyzed at the time. Although the possibility of a malignancy is not eliminated, before proceeding with an invasive biopsy, conservative management should be first attempted.

The patient was empirically started on IV methylprednisolone 100 mg daily for 3 days, followed by oral prednisone 60 mg daily. She was seen in the neuro-ophthalmology clinic 10 days later, where she reported her diplopia had significantly improved and she had only a 2-diopter esophoria on the right gaze. IgG subclass testing showed normal IgG1, 2, and 3; however, IgG-4 was 97.1 (normal 4–86 mg/dL), and total IgG was 1,914 (normal 700–1,600 mg/dL). She was maintained on prednisone 60 mg daily, and a month later, she reported complete resolution of her diplopia. Repeat orbital imaging at the 4-month interval showed resolution of the abnormal enhancement in the orbital apex (Figure 1, B.a–B.c).

## Discussion

IgG-4-related disease (IgG4-RD) is an immune-mediated multiorgan disease that is usually characterized by dense infiltration of tissue with IgG-4-positive plasma cells, which can be accompanied by fibrosis and eosinophilia. Elevated levels of serum IgG4 are seen in most of these patients. Clinical presentations include sclerosing cholangitis, autoimmune pancreatitis, salivary gland disease, retroperitoneal fibrosis, and ophthalmic involvement, among others.<sup>1</sup> In contrast to other autoimmune conditions, the disease has a male predominance and a mean age of 40–70 years. Women are likely

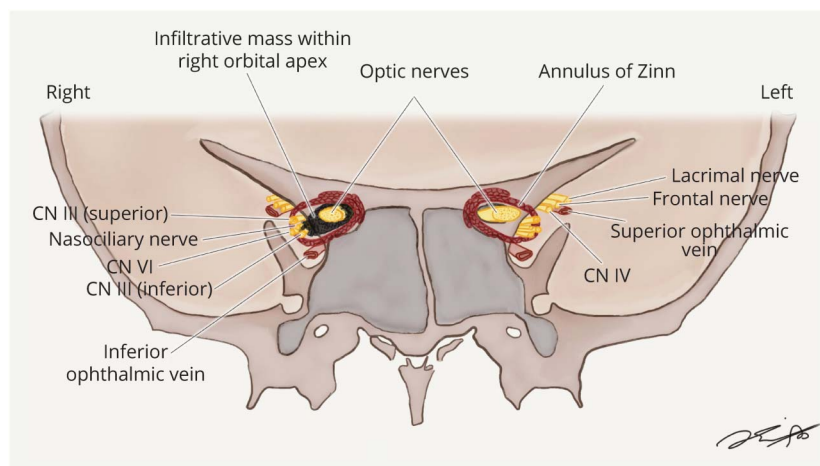
to have superficial organ involvement as opposed to men having internal organ pathology.<sup>2</sup>

Neurologically, IgG4-RD can involve the CNS, meninges (especially the pachymeninges), peripheral nerves, pituitary gland, and orbits. In some cases, proptosis may also be seen because of the inflammation of extraocular muscles causing orbital pseudotumor. IgG4-RD is responsible for up to 50% of cases of orbital pseudotumor. Elevation of serum IgG4, IgG1, and IgE, as well as low C3 and C4, can help support the diagnosis. The patient met the criteria for possible IgG4-RD based on her localized infiltrate within the orbit and elevated total IgG and IgG4 levels (eAppendix 2, [links.lww.com/WNL/C247](https://links.lww.com/WNL/C247)).<sup>3</sup> By the time she was seen in the neuro-ophthalmology clinic and IgG subset levels were tested, they have already begun to improve after treatment. Because the total IgG level was far higher before treatment, it can be assumed that her IgG4 level was higher as well.

Treatment of IgG4-RD is commonly performed with corticosteroids, typically prednisone at a daily dosage of 0.6 mg/kg. It may take 2–4 weeks for a response to become apparent. Once there is improvement, steroids can be gradually tapered off. Rituximab can be used when glucocorticoids are contraindicated or in recurrent disease.<sup>4</sup> Monitoring for disease activity can be performed clinically and through serologic testing every 6 months. Surgical intervention may be indicated in certain cases in which there may be mechanical obstruction and medical management is not effective. The prognosis of IgG4-RD is variable but is a chronic disease in most patients.<sup>5</sup> There are reports associating IgG4-RD with malignancy, but most studies have shown no increased risk.<sup>6</sup>

Our patient had good response to prednisone and did not require a biopsy. To date, she remains symptom free without

**Figure 2** An Illustration Depicting the Orbital Apices at the Craniofacial Junctions With the Inflammatory Mass Infiltrating the Right Apex and Impinging on the Exiting Abducens Nerve, Inferior Division of the Oculomotor Nerve, and the Nasociliary Nerve



recurrence. It is possible that her prior episode of pressure within the right eye was a presentation of IgG4-RD rather than sinusitis. This case highlights the importance of localization and reliance on the neurologic examination because the initial interpretation of the MRI was misleading. Although her pathology within the orbit was small, it was strategically located within the orbital apex causing focal neuropathies (Figure 2). The infiltrate may have caused hyperintensity within the optic nerve on MRI; however, clinically, the patient had no signs or symptoms of an optic neuropathy.

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Name	Location	Contribution
<b>Gaurav Kathuria, MD</b>	Neuroscience Institute, Memorial Healthcare System, Hollywood, FL	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data

### Appendix (continued)

Name	Location	Contribution
<b>Brandi Baker, MD, PhD</b>	Neuroscience Institute, Memorial Healthcare System, Hollywood, FL	Drafting/revision of the manuscript for content, including medical writing for content, and analysis or interpretation of data
<b>Bruce Braffman, MD</b>	Department of Diagnostic Imaging, Memorial Regional Hospital, Hollywood, Florida	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; and analysis or interpretation of data
<b>Adnan M Subei, DO</b>	Neuroscience Institute, Memorial Healthcare System, Hollywood, FL	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data

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