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Dissociation Between Recovery of Ocular Motility and Visual Function in Orbital Apex Syndrome Due to Myeloperoxidase-Antineutrophil Cytoplasmic Antibody-Associated Hypertrophic Pachymeningitis

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Ryusuke Hashimoto [1], Soya Ooka [1], Tomomi Kaiho [1], Takayuki Baba [1]

1. Department of Ophthalmology and Visual Science, Chiba University Graduate School of Medicine, Chiba, JPN

Corresponding author: Ryusuke Hashimoto, ryuhash0421@gmail.com

Abstract

In antineutrophil cytoplasmic antibody (ANCA)-associated hypertrophic pachymeningitis (HP), inflammation can extend to the orbital apex and cause severe visual impairment. A 66-year-old man was hospitalized elsewhere for diabetic ketoacidosis due to untreated diabetes. Although his general condition stabilized, he developed rapidly progressive visual loss in both eyes and was referred to our hospital. At presentation, visual acuity was hand motion in the right eye and no light perception in the left eye. Ocular motility was limited in all directions in both eyes, with proptosis of the left eye. Contrast-enhanced magnetic resonance imaging showed skull-base dural thickening, soft-tissue lesions at both orbital apices, and marked mucosal thickening of the paranasal sinuses. Myeloperoxidase (MPO)-ANCA was positive. Orbital apex syndrome due to MPO-ANCA-associated HP was diagnosed, and he was treated with intravenous methylprednisolone pulse therapy, rituximab, and oral prednisolone. Ocular motility improved markedly; however, at 54 weeks, corrected visual acuity in the right eye had improved only to 0.02 (decimal), and the left eye had no light perception throughout. We report this dissociation between the courses of ocular motility and visual function and discuss its possible mechanisms.

Categories: Neurology, Ophthalmology, Allergy/Immunology
Keywords: anca-associated vasculitis, hypertrophic pachymeningitis, myeloperoxidase-anca, ophthalmoplegia, optic neuropathy, orbital apex syndrome

Introduction

Hypertrophic pachymeningitis (HP) is an inflammatory thickening of the dura mater that can be caused by antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). Most patients with myeloperoxidase (MPO)-ANCA-positive HP are classified as having granulomatosis with polyangiitis (GPA) by the Watts algorithm, and many have a limited form confined to the dura mater and upper airways [1]. In a Japanese registry of 663 patients with AAV, HP occurred in 4.5% and was associated with sudden visual loss [2].

Orbital apex syndrome consists of optic neuropathy accompanied by ophthalmoplegia and has inflammatory, infectious, neoplastic, vascular, and traumatic causes [3]. In a systematic review of ANCA-associated pachymeningitis, visual loss was reported in 25% of patients, diplopia in 20%, and orbital apex involvement on imaging in 10%. Complete clinical recovery was achieved in 46% of patients, although recovery of vision was not reported separately. Diagnosis can be difficult because typical pathological features were found in only about two-thirds of biopsied patients, and the disease shares features with immunoglobulin G4 (IgG4)-related pachymeningitis [4].

The optic nerve, a central nervous system tract, and the oculomotor, trochlear, and abducens nerves, which are peripheral nerves, all pass through the orbital apex [3] but differ in their capacity to recover from injury [5]. Recovery of ocular motility and recovery of vision therefore need not be parallel; ophthalmoplegia improved while vision did not in a patient with MPO-ANCA-positive pachymeningitis [6] and in a patient with GPA [7]. We report a patient in whom this dissociation was documented over approximately one year with serial nine-gaze photographs and visual acuity measurements, and we discuss its possible mechanisms and implications for monitoring visual function.

Case Presentation

A 66-year-old man with a three-month history of weight loss of approximately 10 kg and worsening general fatigue was taken by ambulance to another hospital when he became unable to move. He was admitted with diabetic ketoacidosis due to untreated diabetes (glycated hemoglobin (HbA1c), 16.4% at that hospital). His general condition improved with treatment. About three months after admission, approximately five weeks

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before presentation to our hospital, he noticed visual loss in the left eye, followed by the right eye, and he was referred to our hospital for further evaluation and treatment.

At presentation (day 0), visual acuity was hand motion (HM) in the right eye and no light perception (NLP) in the left eye. Both pupils were dilated and nonreactive to light, precluding assessment of a relative afferent pupillary defect. The left eye had ophthalmoplegia in all directions, and the right eye had a severe abduction deficit with limitation in the other directions (Figure *1A*).



FIGURE 1: Nine-gaze photographs.

Each panel shows nine photographs arranged as seen by the examiner: the top, middle, and bottom rows show upgaze, horizontal gaze, and downgaze, and the left and right columns show right and left gaze, respectively. The center photograph shows the primary position, and arrows indicate the direction of gaze. (A) Day 0: ocular motility is severely limited in all directions in the left eye, and the right eye has a severe abduction deficit with limitations in the other directions. (B) Week 24: there is no limitation of ocular motility in either eye. In some images, the examiner is holding up the upper eyelids.

Hertel exophthalmometry measured 13 mm in the right eye and 18 mm in the left eye (base, 112 mm). Ultra-widefield fundus photography (Optos, Dunfermline, UK) and spectral-domain optical coherence tomography (OCT) line scans (Spectralis, Heidelberg Engineering, Heidelberg, Germany) showed no diabetic retinopathy, optic disc swelling, retinal whitening, inner retinal hyperreflectivity, or macular edema in either eye (Figure *2*).

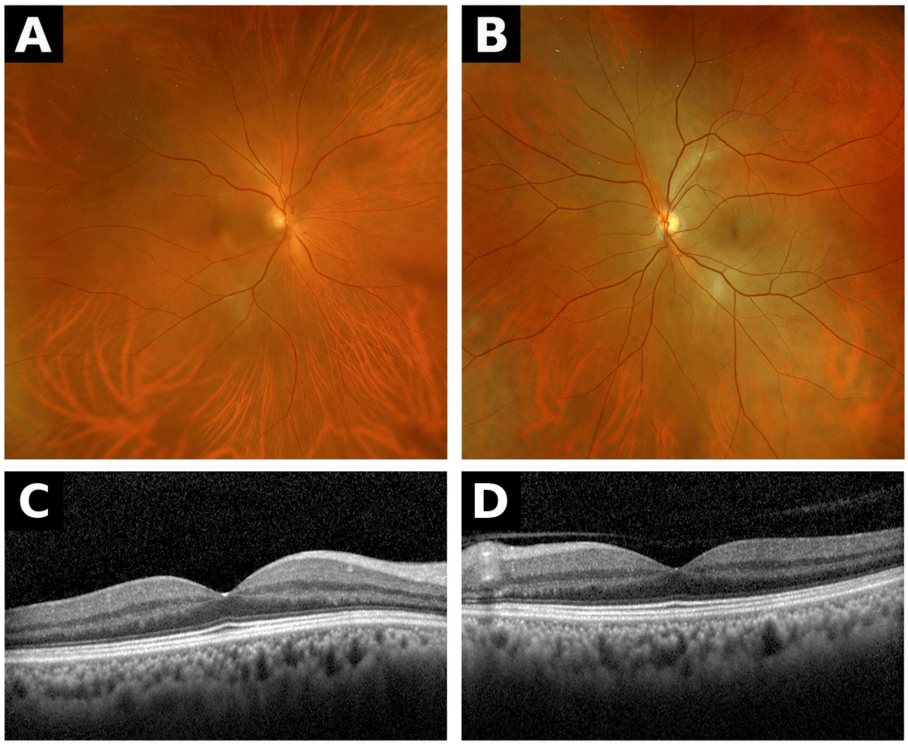


FIGURE 2: Fundus photographs and optical coherence tomography (OCT) at presentation.

Ultra-widefield fundus photographs (Optos) of the right (A) and left (B) eyes show no optic disc swelling or retinal whitening. Horizontal OCT line scans through the fovea (Spectralis) of the right (C) and left (D) eyes show no inner retinal hyperreflectivity or macular edema.

He had left facial pain and a headache but no jaw claudication. Contrast-enhanced magnetic resonance imaging on day 0 showed skull-base dural thickening (Figure *3A*) and soft-tissue lesions at both orbital apices, more prominent on the left (Figure *3B*). There was also marked mucosal thickening of the paranasal sinuses (Figure *3C*), enhancement of the nasal septum, and fluid in the left mastoid air cells. Neither optic nerve showed definite enhancement. Lacrimal gland enlargement was present, whereas infraorbital nerve thickening and salivary gland enlargement were not evident.

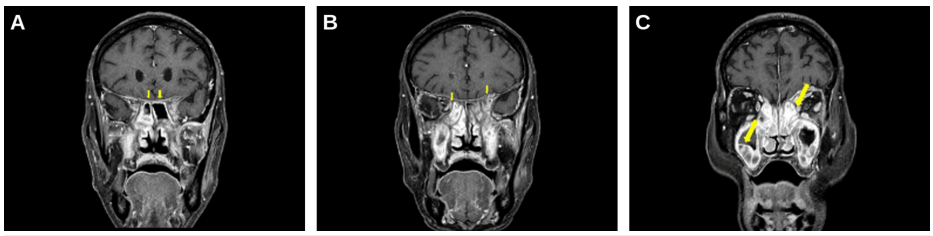


FIGURE 3: Contrast-enhanced T1-weighted coronal magnetic resonance images of the head (skull base, orbits, and paranasal sinuses) at presentation.

(A) Skull-base dural thickening (arrows). (B) Enhancement at both orbital apices (arrows). (C) Marked mucosal thickening of the paranasal sinuses (arrows).

The MRI findings prompted tests to distinguish AAV from IgG4-related disease and from infection, particularly fungal infection. Laboratory tests showed positive MPO-ANCA (26.8 U/mL), negative proteinase 3 (PR3)-ANCA, elevated C-reactive protein (9.82 mg/dL) and erythrocyte sedimentation rate (71 mm/h), an HbA1c of 10.4%, and a normal serum IgG4 level (86.8 mg/dL). Cerebrospinal fluid (CSF) analysis showed a cell count of 1/μL and an elevated protein level of 109 mg/dL. Serum and CSF beta-D-glucan, serum Aspergillus and cryptococcal antigens, and anti-aquaporin-4 antibody (enzyme-linked immunosorbent assay) were negative.

Nasal mucosal biopsies were taken from approximately seven sites at presentation. They showed stromal lymphocytic infiltration without definite vasculitis, and immunohistochemistry and Epstein-Barr virus-encoded small RNA in situ hybridization (EBER-ISH) showed no definite neoplastic change. Fungal stains and IgG4 immunostaining were not performed.

AAV was considered most likely because of MPO-ANCA positivity, elevated inflammatory markers, and dural and sinonasal involvement. Invasive fungal disease was considered less likely because serum and CSF fungal markers were negative and because his condition later improved with immunosuppressive therapy without antifungal treatment. IgG4-related disease was considered less likely because serum IgG4 was normal. Based on these findings, we made a clinical diagnosis of orbital apex syndrome due to MPO-ANCA-associated HP.

Diabetic ketoacidosis had resolved, and HbA1c had decreased from 16.4% to 10.4%. Because high-dose glucocorticoids could worsen glycemic control, treatment was co-managed with diabetologists, and blood glucose remained well controlled throughout. Intravenous methylprednisolone pulse therapy (1,000 mg/day for five days) was started on day 3, followed by oral prednisolone at 55 mg/day (approximately 1 mg/kg). Prednisolone was tapered by 5 mg weekly to 30 mg/day at week 6 and then tapered further; the dose was 10 mg/day at week 54. Rituximab 600 mg (375 mg/m^2, adjusted to vial size) was given weekly for four doses starting at week 1, followed by maintenance doses of 600 mg every six months.

Ocular motility improved markedly by week 2, and full ductions were recorded from week 5 (Figure *1B*). Visual acuity in the right eye improved from HM to 0.01 (0.02 with correction; decimal) by week 2 and remained unchanged through the last visit at week 54. The left eye had NLP from day 0 to the last visit (Figure *4*).

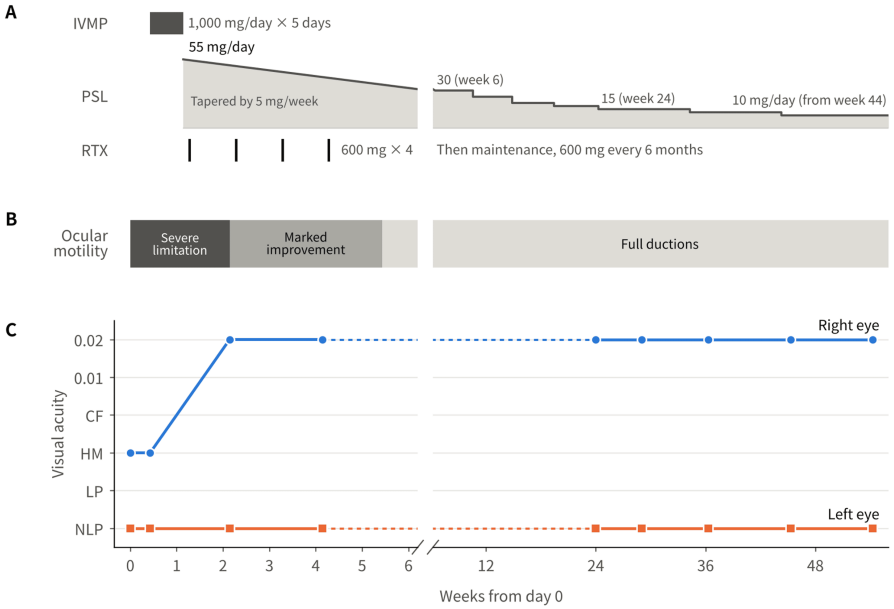


FIGURE 4: Clinical course.

(A) Treatment. The PSL line shows the daily dose; the taper of 5 mg per week until week 6 is drawn as a straight line. After four weekly doses, RTX was continued as maintenance therapy at 600 mg every six months. (B) Ocular motility, based on clinical records: severe limitation at presentation (complete ophthalmoplegia in the left eye), marked improvement by week 2, and no limitation recorded from week 5 onward. (C) Visual acuity (decimal). Only measurements obtained in the ophthalmology department are shown, and corrected acuity is plotted when correction improved it. The vertical axis is ordinal, and its intervals do not represent differences in acuity. Occasional HM and LP responses in the left eye and transiently lower values in the right eye were judged unreliable; the left eye is shown as NLP throughout, and the right eye as corrected 0.02 from week 2. Dotted lines indicate intervals without measurements. The horizontal axis shows weeks from day 0 (presentation), with a scale break at week 6.

IVMP, intravenous methylprednisolone; PSL, oral prednisolone; RTX, rituximab; NLP, no light perception; LP, light perception; HM, hand motion; CF, counting fingers.

Discussion

In our patient, ocular motility improved markedly within weeks of immunosuppressive treatment, whereas visual acuity barely improved from presentation. A similar dissociation has been reported in ANCA-associated orbital apex disease. Choi et al. described a 79-year-old woman with MPO-ANCA-positive pachymeningitis and bilateral orbital apex syndrome whose ophthalmoplegia improved with glucocorticoids and cyclophosphamide while vision did not, and diffuse optic atrophy was present at one year [6]. Chua and Lim reported a patient with PR3-ANCA-positive GPA whose ocular motility partially recovered while vision declined to NLP, mainly because of irreversible ischemic optic neuropathy and extensive corneoscleral melt [7]. Ophthalmoplegia also recovers more often than vision in orbital apex syndrome caused by invasive fungal rhinosinusitis or trauma [8,9]. Nevertheless, the visual outcome is not always poor. Murai et al. described an MPO-ANCA-positive patient with bilateral orbital apex syndrome associated with sinusitis who regained normal vision after steroid pulse therapy and early endoscopic sinus surgery with optic canal decompression [10]. We considered three factors that may explain the dissociation in our patient: differences in the regenerative capacity of the injured nerves, the anatomical and vascular vulnerability of the optic nerve, and the severity and duration of optic nerve injury at the start of treatment.

The first factor is the difference in regenerative capacity between the injured nerves. The oculomotor, trochlear, and abducens nerves pass through the superior orbital fissure at the orbital apex [3] and, unlike the optic nerve, are peripheral nerves. Peripheral nerves can regenerate and recover function even after axonal injury [5], and inflammatory or compressive dysfunction without axonal injury can resolve as inflammation subsides. In contrast, the optic nerve is a central nervous system tract composed of retinal ganglion cell axons, and axon regeneration in the mature central nervous system is extremely limited [5]. The early improvement in ocular motility suggests that the ophthalmoplegia was due mainly to dysfunction that was reversible once inflammation subsided. The accompanying lacrimal gland enlargement suggests that orbital inflammation was not confined to the apex, and inflammation of other orbital tissues may also have contributed to the ophthalmoplegia.

The second factor is the anatomical and vascular vulnerability of the optic nerve. At the orbital apex and

within the optic canal, the optic nerve runs in its dural sheath through a narrow bony space, which makes it susceptible to compression by surrounding soft-tissue lesions and dural thickening [3,6]. In addition, the posterior part of the optic nerve is supplied mainly by the pial vascular plexus, and circulatory impairment in this segment causes posterior ischemic optic neuropathy, which presents with visual loss without optic disc swelling [11]. Our patient had severe visual loss in both eyes without disc swelling, retinal whitening, or inner retinal hyperreflectivity, and soft-tissue lesions were present at both orbital apices. These findings, together with the absence of fundus or OCT signs of retinal artery occlusion or anterior ischemic optic neuropathy, suggest retrobulbar optic neuropathy at the orbital apex caused by inflammation, compression, ischemia, or a combination of these. The more severe involvement of the left eye, with NLP, ophthalmoplegia in all directions, and proptosis, corresponded to the more prominent soft-tissue lesion at the left orbital apex. AAV-related vasculitis itself may have contributed to ischemia, but the relative contributions of these mechanisms cannot be determined in our patient.

Whatever the mechanism, vision is unlikely to recover once substantial axonal loss has occurred, because retinal ganglion cell axons regenerate poorly [5]. In chiasmal compression by parachiasmal tumors, for example, patients with retinal nerve fiber layer thinning before surgical decompression were less likely to regain visual acuity or visual field [12].

The third factor is the severity and duration of optic nerve injury at the start of treatment. About five weeks had elapsed between the onset of visual symptoms and the start of treatment, and visual acuity at presentation was already HM in the right eye and NLP in the left eye. In inflammatory orbital apex syndrome, the interval from symptom onset to steroid administration tended to be longer in patients whose vision did not improve, although the difference was not statistically significant [13]. In orbital apex syndrome due to invasive fungal rhinosinusitis, visual acuity recovered to better than 20/200 in 4 of 20 patients with initial acuity worse than 20/200, and all 4 were among the 12 patients in whom the interval to treatment was less than four weeks [8]. The slight improvement in the right eye, from HM to corrected 0.02, in contrast to persistent NLP in the left eye, may also reflect a difference in the severity of injury between the two eyes.

Taken together, the dissociation in our patient may have resulted from the coexistence of ocular motor dysfunction that was reversible once inflammation subsided and optic nerve injury that had probably become irreversible before treatment began. Disease activity, ocular motility, and visual function should be assessed separately, because improvement in one does not necessarily mean improvement in the others. When visual loss develops in patients with AAV and orbital apex involvement, prompt treatment before optic nerve injury becomes irreversible appears to be important.

Limitations

The diagnosis in our patient was clinical. Nonspecific nasal biopsy findings are common in GPA and do not exclude it [14], but our biopsy did not provide histological confirmation, and no sphenoid, orbital, or dural tissue was obtained. Because of poorly controlled diabetes and sinus disease, infection, particularly fungal infection, had to be excluded; fungal infection is a recognized cause of orbital apex syndrome in patients with poorly controlled diabetes [3]. Negative serum and CSF beta-D-glucan and serum fungal antigen tests do not exclude invasive fungal disease, and fungal stains were not performed. Lacrimal gland enlargement also occurs in IgG4-related disease, which cannot be excluded on the basis of a normal serum IgG4 level without tissue IgG4 staining. Giant cell arteritis was not specifically excluded. The absence of disc swelling on day 0 argued against arteritic anterior ischemic optic neuropathy, although swelling may already have resolved. Arteritic posterior ischemic optic neuropathy, which occurs without disc swelling, also cannot be excluded [11]. In addition, no vasculitis subtype was assigned. Classification of MPO-ANCA-positive HP as GPA by the Watts algorithm relies mainly on surrogate markers such as chronic sinusitis [1], whereas patients with HP in the Japanese registry (77% MPO-ANCA-positive) were evenly divided between GPA and microscopic polyangiitis [2]. Classification algorithms, however, do not replace clinical diagnosis [14].

Furthermore, in AAV-related HP, rituximab has been associated with radiological improvement [15] and, when used as first-line therapy, with fewer refractory cases [4]. Because our patient received glucocorticoids and rituximab concurrently, however, the effect of each agent cannot be isolated. Ductions were not graded quantitatively at the time of examination, so the improvement in ocular motility is documented by the nine-gaze photographs rather than by graded measurements. Finally, the mechanisms discussed here are inferences from a single patient. They could not be confirmed, because visual evoked potentials, diffusion-weighted imaging of the optic nerves, and optic nerve histopathology were not obtained.

Conclusions

In this patient with orbital apex syndrome due to MPO-ANCA-associated HP, ocular motility improved substantially after immunosuppressive treatment, whereas visual acuity remained severely reduced in both eyes. This dissociation may reflect the difference between reversible ocular motor dysfunction and optic nerve injury that had probably become irreversible before treatment, although this mechanism could not be confirmed. In patients with AAV and orbital apex involvement, visual function should be monitored as an independent outcome rather than being inferred from improvement in ocular motility or regression of

orbital inflammation.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Ryusuke Hashimoto, Soya Ooka, Tomomi Kaiho

Acquisition, analysis, or interpretation of data: Ryusuke Hashimoto, Tomomi Kaiho, Takayuki Baba

Drafting of the manuscript: Ryusuke Hashimoto, Soya Ooka, Tomomi Kaiho

Critical review of the manuscript for important intellectual content: Ryusuke Hashimoto, Soya Ooka, Takayuki Baba

Supervision: Tomomi Kaiho, Takayuki Baba

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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