

# Cyclosporine-Associated Leukoencephalopathy in a Case of Sympathetic Ophthalmitis

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## Key Words

Cyclosporine · Posterior reversible encephalopathy syndrome · Sympathetic ophthalmitis

## Abstract

**Purpose:** Cyclosporine (CsA) is currently widely used as a primary immunosuppressive agent in ocular disease, particularly in severe uveitis. Posterior reversible encephalopathy syndrome (PRES) is a significant complication of CsA therapy. However, there are no reports of the occurrence of PRES in response to the treatment of uveitis in the ophthalmological area. **Case Presentation:** We report a case with CsA-associated PRES. A 70-year-old woman with sympathetic ophthalmitis was treated with 50 mg/day of CsA for 1 week. However, the trough level in her blood was too low; thus, we increased the dose to 100 mg/day of CsA with prednisolone. She had headaches, hypertension (systolic blood pressure 180–200 mm Hg), loss of consciousness for several hours, and reduced limb movement, and her MRI showed a high signal intensity in both posterior lobes, consistent with PRES. Examination of the cerebrospinal fluid indicated that it was within normal limits. Her CsA trough level in the blood was within normal ranges on the day of the attack. Her symptoms gradually improved over the next several days; however, she presented with cortical blindness, which lasted for several weeks. Finally, she returned to her baseline values from before the attack. Her MRI findings showed that PRES had essentially disappeared. **Conclusion:** PRES is not directly associated with the dosage of CsA administered; however, in general, it is well known that PRES can affect strongly immunosuppressed cases undergoing organ and bone marrow transplantation. Nevertheless, our CsA dose was only 100 mg (1.8 mg/kg). In this study, we report on the occurrence of PRES after the administration of CsA to treat sympathetic ophthalmia. To our knowledge, PRES can also occur after the administration of a small dose of CsA; thus, ophthalmologists using CsA should carefully observe the systemic conditions of CsA-treated patients.

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## Introduction

Immunosuppressive treatment-associated leukoencephalopathy is a significant complication of cyclosporine (CsA) therapy [1]. CsA is currently widely used as a primary immunosuppressive agent in ocular disease, particularly in severe uveitis [2].

Posterior reversible encephalopathy syndrome (PRES) is reversible and occurs in the white matter of the occipital lobe and ventricle neighborhood. PRES leads to pathological changes, such as high blood pressure, to immunosuppressive conditions, such as encephalopathy, and is a diffuse collagen disease; CsA administration has been shown to be a cause of PRES.

PRES is not directly associated with the dosage of CsA administered; however, in general, it is well known that PRES can affect strongly immunosuppressed cases undergoing organ and bone marrow transplantation [1]. Nevertheless, our CsA dose was only 100 mg (1.8 mg/kg).

In this study, we report on the occurrence of PRES after the administration of CsA to treat sympathetic ophthalmia. To our knowledge, this is the first report of the occurrence of CsA-induced PRES in response to treatment for uveitis in the ophthalmological area.

## Case Report

A 70-year-old woman was treated for acute retinal necrosis in both eyes 15 years ago with pars plana vitrectomy and lensectomy without intraocular lens implantation at that time. She was referred by her family doctor for evaluation and treatment of progressive retinal detachment in the right eye. Her past medical history was significant only for hypertension, which was well controlled with oral Ca blockers.

Her best corrected visual acuity (BCVA) was 0.02 OU. She had immediate pars plana vitrectomy with scleral buckling with silicone oil tamponade. However, she went blind in her right eye after 3 months. Two months later, she had blurred vision in her left eye. Her BCVA OS was 0.02, and her intraocular pressure was 12 mm Hg OS. Slit-lamp examination demonstrated cells, flare, and mutton-fat keratic precipitates in the anterior chamber, strong vitreous cavity opacification, and vitreous cells. Fundus examination was difficult because of opacification (fig. 1a). We detected swelling of the choroid, and optical coherence tomography showed serious retinal detachment at the posterior pole. Fluorescein angiography showed leakage corresponding to serious retinal detachment areas (fig. 1b). The results of the laboratory investigations of the serum including angiotensin-converting enzyme, antinuclear antibodies, rheumatoid factor, and antineutrophil cytoplasmic antibodies were unremarkable except for the presence of elevated C-reactive protein. Serological analyses indicated that there was no active infection of syphilis, human T-cell lymphoma virus 1, herpes simplex virus, or varicella zoster virus. We diagnosed sympathetic ophthalmitis.

The patient then received steroid pulse therapy (1,000 mg/day of methylprednisolone for 3 days/week), followed by 30 mg/day of prednisolone therapy administered orally. However, her intraocular inflammation could not be stabilized, particularly the opacification in the vitreous cavity. Thus, we added 50 mg/day of CsA for 1 week; however, the trough level in her blood was too low, so we increased the dose to 100 mg/day of CsA with 10 mg/day of prednisolone. In addition, her systolic blood pressure was too low (approximately 85–100 mm Hg with no symptoms), so we ceased the administration of Ca blockers for her hypertension (fig. 2).

Two days later, she displayed a sudden onset of headache and hypertension (systolic blood pressure 180–200 mm Hg), loss of consciousness for several hours, and reduced limb movement. We speculated acute or subacute onset brain infarction; thus, we immediately performed a head MRI. The radiologist first diagnosed acute brain infarction. However, a neurologist in another hospital noted the possibility of PRES. The MRI showed a high signal intensity in both posterior lobes, consistent with PRES (fig. 3a). An electroencephalogram showed diffuse slow and irregular ground activity (data not shown). An examination of the cerebrospinal fluid indicated that it was within normal limits. Her CsA trough level in the blood was 68 ng/ml on the day of the attack.

CsA use was immediately stopped. Her blood pressure was strictly managed in the ICU of the Neurology Department. Her symptoms gradually improved over the next several days; however, she developed cortical blindness, which lasted for several weeks. Finally, she returned to her baseline state before the attack, including her BCVA. The MRI findings with axial views showed that hyperintense spots remained on both posterior lobes 6 months after the day of the attack (fig. 3b). Ocular inflammation could be stabilized by oral prednisolone (fig. 1c, d).

## Discussion

Posterior encephalopathy and toxemic posterior encephalopathy were first described by Hinchey et al. [1] in 1996.

Although PRES patients may have hypertension, this is not always the case [3–5].

Etiological factors for PRES include hypertension; eclampsia-preeclampsia; immunosuppressant and chemotherapeutic medications such as CsA, tacrolimus, interferon- $\alpha$ , and corticosteroids; renal diseases such as lupus nephritis, acute glomerulonephritis, hemolytic uremic syndrome, and thrombotic thrombocytopenic purpura; transplantations; infections including influenza A, sepsis, shock, and toxemia; pregnancy; autoimmune diseases, and some vaccinations such as measles. Eclampsia might be a good prognostic factor for PRES [6–9].

Although the detailed mechanisms underlying PRES are not yet clear, some theories have been suggested. Currently, the most widely accepted theory suggests that severe hypertension leads to failed autoregulation, which subsequently causes hyperperfusion with endothelial injury/vasogenic edema [6].

The use of CsA for the treatment of uveitis was first reported in 1983 [10].

In many studies, the efficacy of CsA has been confirmed in idiopathic uveitis, Vogt-Koyanagi-Harada disease, birdshot retinochoroidopathy, serpiginous choroiditis, panuveitis, and Behçet's disease [2, 10–13].

In Japan, CsA is currently available for endogenous uveitis, particularly for Behçet's disease [14]; however, there are no large statistical reports of severe side effects, such as PRES. Even if PRES has been identified as a side effect, it is rarely experienced by ophthalmologists. In this report, PRES appeared after the administration of a low dosage of CsA (50–100 mg), which is a commonly used dosage, for example, to treat atopic dermatitis [15]. In general, a small amount of CsA is prescribed (50–100 mg/day).

Ophthalmologists generally believe that CsA-induced PRES only rarely occurs. However, it has also been reported that PRES is unrelated to the dosage of CsA administered.

Our study demonstrates that PRES occurred after the administration of only a small amount of CsA. This may be because CsA was combined with prednisolone or because blood pressure was poorly controlled at the onset.

In conclusion, we reported CsA-associated leukoencephalopathy in a case of sympathetic ophthalmitis. Several questions remain, such as the development mechanism and the long-term prognosis. Fortunately, our patient recovered almost completely, despite the fact that PRES can have severe long-term effects. CsA, even a small dose, can induce PRES when it is prescribed for the treatment of uveitis. Therefore, ophthalmologists prescribing CsA should carefully observe the systemic conditions, particularly the blood pressure, of CsA-treated patients.

### Acknowledgements

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### Statement of Ethics

Written informed consent was obtained from the patient.

### Disclosure Statement

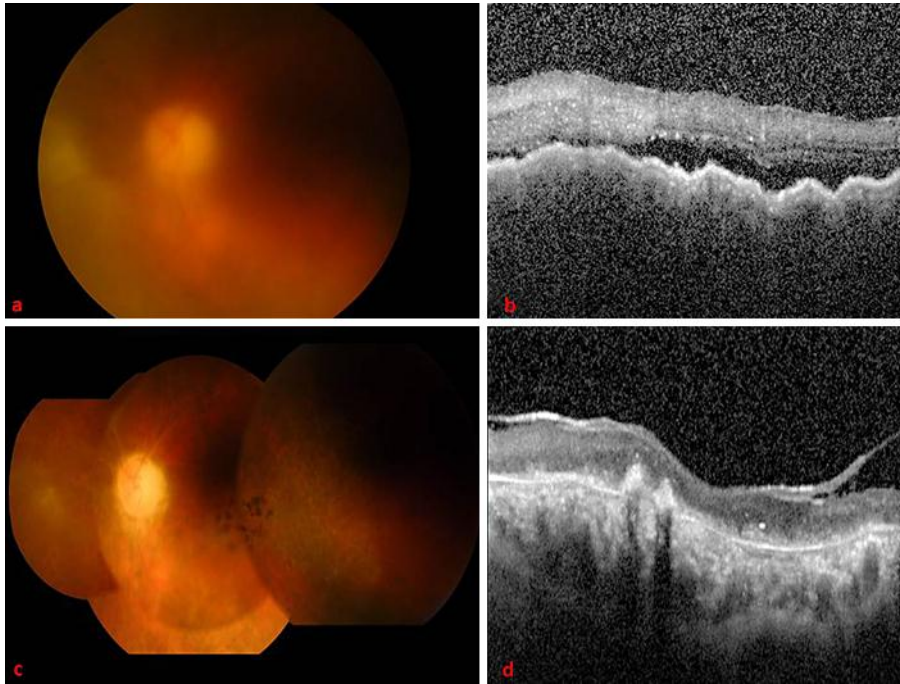
None of the authors has any proprietary or financial interests.

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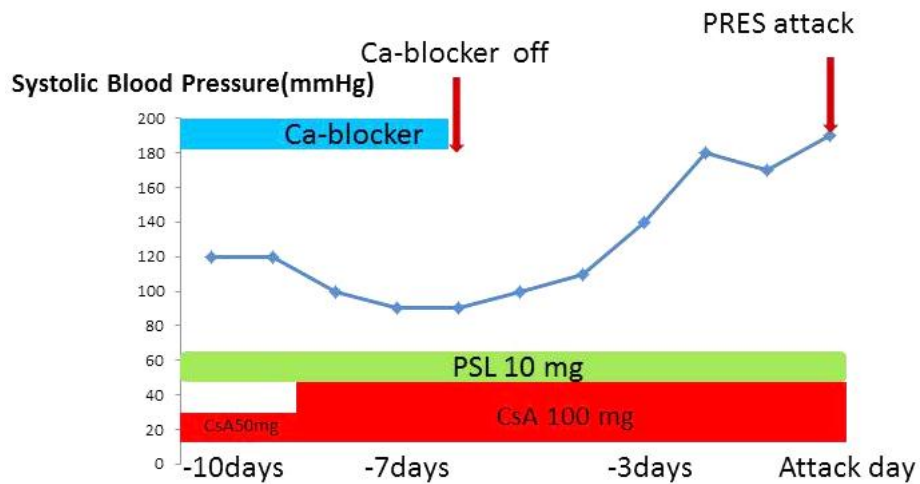
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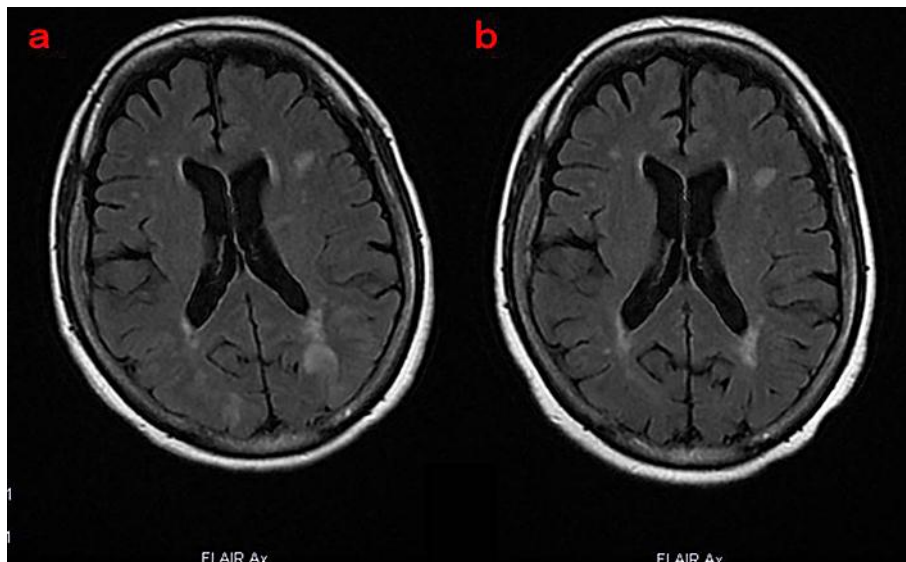
**Fig. 1.** **a** Fundus photography before any treatment. The fundus is nearly invisible because of the opacification of the vitreous cavity. **b** Optical coherence tomography shows choroidal folds and serious retinal fluid near the posterior pole. **c** Fundus photography after 6 months of treatment. The fundus is nearly clear. **d** Optical coherence tomography shows the disappearance of choroidal folds and serious retinal fluid near the posterior pole.



## Clinical time course



**Fig. 2.** Clinical time course. Administration of Ca blockers was ceased because the patient's systolic blood pressure was much too low; after the attack, it increased significantly and was too high. PSL = Prednisolone.



**Fig. 3.** MRI shows hyperintense imaging on T2. Fluid-attenuated inversion recovery sequences. **a** Axial views show hyperintensity on both posterior lobes on the day of the attack. **b** Axial views show that dot hyperintensity spots remain on both posterior lobes 6 months after the day of the attack.