



Anterior uveitis and multiple sclerosis

DAVID M. MEISLER, MD; ROBERT L. TOMSAK, MD, PHD; SAMIA KHOURY, MD; MAURICE R. HANSON, MD;
IVAN R. SCHWAB, MD; RICHARD M. RANSOHOFF, MD

■ Three patients with clinically definite multiple sclerosis and uveitis were studied. The uveitis presented as inflammation of the anterior segment of the eye (iridocyclitis) and was characterized by large keratic precipitates and posterior synechiae, consistent with a granulomatous iridocyclitis. Clinical and laboratory evidence militated against other central nervous system diseases often associated with uveitis including neurosarcoidosis, Behçet's syndrome, Vogt-Koyanagi-Harada disease, neurosyphilis, and tuberculosis. Further attention should be directed to the possibility of granulomatous anterior uveitis in patients with multiple sclerosis.

□ INDEX TERMS: IRIDOCYCLITIS; MULTIPLE SCLEROSIS; UVEITIS □ CLEVE CLIN J MED 1989; 56:535-538

MULTIPLE sclerosis (MS) is a central nervous system (CNS) disorder in which tissue injury appears to be mediated in part by autoimmune mechanisms.¹ The most common form of ocular inflammation associated with multiple sclerosis is optic neuritis.² Another form of ocular inflammation, uveitis, has less commonly been associated with MS.³⁻⁷ In clinical series to date uveitis involving the anterior segment of the eye (iridocyclitis) in MS has been uncommon and usually mild.

We report on three patients with multifocal neurological disease fulfilling the Poser criteria for clinically definite MS.⁸ All had signs of anterior uveitis. In addition the inflammation had the clinical appearance of a chronic "granulomatous" iridocyclitis.

From the Departments of Ophthalmology (D.M.M.), Neurology (M.R.H., R.M.R.), and the Mellen Center for Multiple Sclerosis Treatment and Research (R.M.R.), The Cleveland Clinic Foundation; Division of Neuro-Ophthalmology (R.T.), Department of Neurology (S.K.), University Hospitals of Cleveland; and Department of Ophthalmology (I.R.S.), West Virginia University Medical Center, Morgantown. Submitted July 1988; accepted Oct 1988.

Address reprint requests to D.M.M., Department of Ophthalmology, The Cleveland Clinic Foundation, One Clinic Center, 9500 Euclid Avenue, Cleveland, Ohio 44195.

PATIENTS

Two patients (Cases 1 and 2) were examined in the Ophthalmology Department of The Cleveland Clinic Foundation (CCF) and the third (Case 3) in the Ophthalmology Department of West Virginia University Medical Center.

Case 1

At age 18, a black woman presented with quadriparesis and bilateral visual disturbance; further details were not available. She was told that she had multiple sclerosis. Her condition then improved considerably over months. Over the next several years, she had relapses, which included gait disturbance and sensory abnormalities; at age 28, generalized seizures developed, for which she was treated with phenytoin. She consulted us in 1976 at age 31 because of an exacerbation of neurological symptoms. At that time she had dysarthria, a visual acuity of 20/25 OD and 20/800 OS, optic atrophy bilaterally, horizontal nystagmus worse on gaze left, ataxic gait, and spastic quadriparesis. Her condition improved partially over several months. At age 38 she complained of decreased visual acuity and ocular tearing and burning. Visual acuity was 20/30 OD and light perception

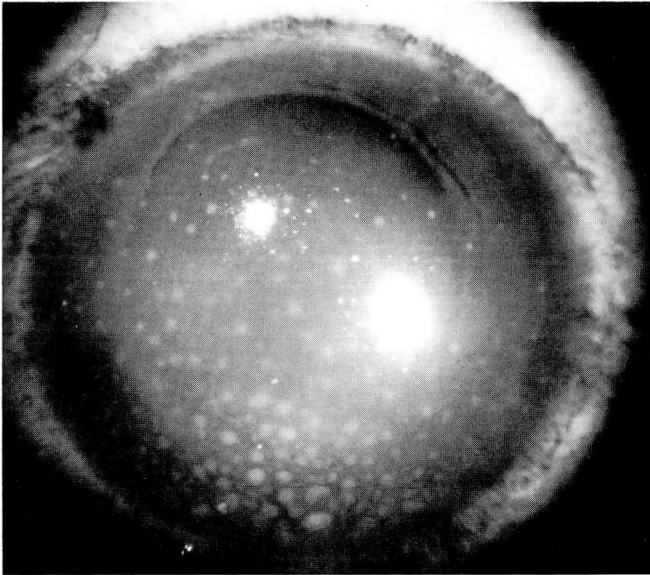


FIGURE 1. Case 1: Slit-lamp photograph demonstrating granulomatous-appearing keratic precipitates.

OS. She was found to have iridocyclitis OS characterized by large white granulomatous-appearing keratic precipitates, anterior chamber cells, and posterior synechiae. Chest radiographs were normal, and a gallium scan showed only minimally increased uptake in the lacrimal and parotid glands. The PPD was positive and serum angiotensin converting enzyme (SACE) was normal. Over the next four years she had numerous documented exacerbations of uveitis in both eyes, which responded to posterior sub-Tenon's injections of triamcinolone and topical steroids. During this period isoniazid and rifampin were prescribed for presumed tuberculosis as the cause of the granulomatous uveitis, however, recurrence of uveitis was observed despite continued antituberculous therapy (Figure 1). When last seen in 1987 (age 42), her visual acuity was 20/40 –1 OD and 20/400 OS. Other neurologic symptoms had remained stable or progressed minimally.

Serologic tests for syphilis were nonreactive on several occasions. Sputum smears and cultures for tuberculosis were repeatedly negative. In 1985, cerebrospinal fluid (CSF) examination showed no erythrocytes, 27 leukocytes/ μL , protein 40 mg/dL, glucose 87 mg/dL, IgG/albumin ratio of 0.67 (normal 0.05–0.17) and daily IgG synthesis rate of 47.4 mg (normal 0–3.7 mg). In 1986, magnetic resonance (MR) imaging of the brain showed periventricular lesions consistent with MS (Figure 2). A conjunctival biopsy showed no abnormalities.

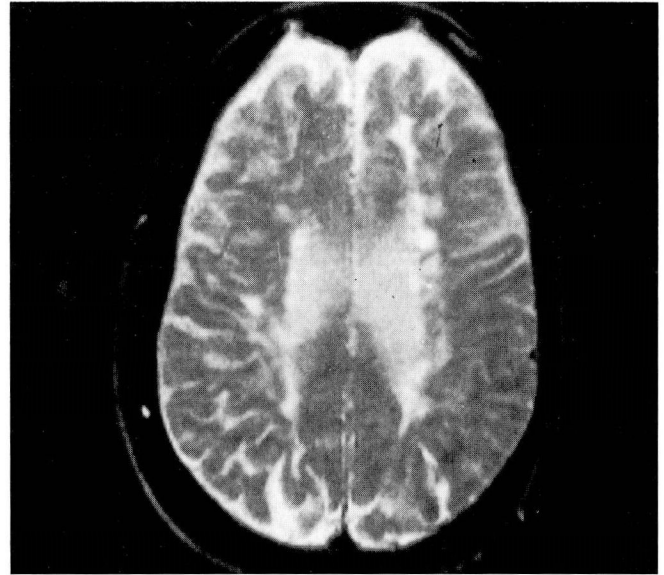


FIGURE 2. Case 3: T2-weighted axial magnetic resonance image showing multiple periventricular areas of increased signal intensity.

Case 2

At age 40 a black woman had onset of a visual disturbance in the right eye. At age 48 (1985) she told us that she had had difficulty writing with her right hand for three months and that she had had loss of control of the left leg and loss of balance for three weeks. Examination at that time showed ataxic dysarthria, ataxic gait, limb dysmetria, and bilateral pyramidal tract abnormalities. Visual acuity was 20/200 OD and 20/400 OS. Granulomatous-appearing keratic precipitates, mild anterior chamber inflammatory reaction OU, and peripheral retinal vascular sheathing OD were seen on slit-lamp examination. The anterior segment inflammation responded to topical steroid therapy. Serologic tests for syphilis were negative; lysozyme, SACE, and chest radiographs were normal. Visual evoked responses were delayed bilaterally, and brain stem auditory evoked responses showed right brain stem dysfunction. Cutaneous testing for anergy showed responses to mumps, trichophyton, and monilia but not to tuberculin. The spinal fluid, under normal pressure, had no erythrocytes, one leukocyte/ μL , protein 25 mg/dL, glucose 62 mg/dL, an IgG/albumin ratio of 0.52, daily IgG synthesis rate of 27.7 mg, and oligoclonal bands were identified in CSF. A cervical myelogram was normal. In 1986, MR imaging of the brain showed multiple periventricular, left cerebellar, and right cerebellar peduncle abnormalities on T2-weighted images. Conjunctival biopsy was normal.

Case 3

In 1966, a 23-year-old white woman developed bilateral lower limb paresthesia. In 1967 she developed left optic neuritis, which produced a large central scotoma lasting three weeks. Later that year, she had two weeks of vertigo, vomiting, and urinary hesitancy. Neurological examination revealed dysarthric speech, right facial weakness, pyramidal tract and cerebellar dysfunction, and decreased appreciation of position changes in the lower limbs. Dementia was present. She improved to a degree, but in 1968, she had nystagmus on lateral gaze to either side as well as the previously noted dysarthria and pyramidal tract and cerebellar dysfunction. Bilateral uveitis was identified in 1972. Chest radiographs showed healed histoplasmosis and skin testing was positive for mumps and histoplasmosis. Vitreous cellular debris was noted in both eyes in 1974. She suffered recurrent episodes of optic neuritis between 1975 and 1977, and in 1976 visual acuity was 20/200 OD and 20/100 OS. In early 1980, slit-lamp examination revealed granulomatous-appearing keratic precipitates. In 1983 the uveitis worsened, and neurological examination showed new left facial weakness, new hypalgesia on the lower limbs, and the pyramidal tract dysfunction, cerebellar dysfunction, and dementia noted previously.

In 1983, a contrast-enhanced CT scan of the head showed periventricular areas of decreased absorption and perhaps periventricular enhancement. The gallium scan was normal and an FTA-abs test was nonreactive. The spinal fluid had no erythrocytes and 38 leukocytes (all mononuclear) per microliter, protein 46 mg/dL, increased IgG/albumin at 0.4, nonreactive serologic test for syphilis, negative cultures, and oligoclonal bands were identified. MR imaging in 1986 showed multiple periventricular areas of increased signal on T2-weighted images. SACE and serum lysozyme levels were within normal ranges.

DISCUSSION

Uveitis is a generic term used to describe intraocular inflammation affecting the uvea (iris, ciliary body, and choroid) and sometimes involving contiguous structures such as the retina and vitreous. One classification of uveitis is based on the anatomic site of inflammation in the eye⁹; for example, uveitis involving the anterior segment of the eye (iritis, iridocyclitis) or uveitis involving the posterior segment of the eye (choroiditis). More recently, the term *intermediate uveitis* has been coined to describe intraocular inflammation mainly concentrated about the ciliary body (cyclitis), in which anterior

chamber reaction is minimal or absent, synechiae (adhesions of iris to other ocular structures) rarely form, and inflammatory cells are present in the anterior vitreous.¹⁰ Retinal periphlebitis, i.e., sheathing of retinal veins, often near the ora serrata (junction of pars plana of the ciliary body with the retina) is also part of the clinical spectrum of intermediate uveitis.

The incidence and significance of uveitis in MS are not well known. Reports have described sheathing of peripheral retinal vasculature occurring in individuals with MS, sometimes associated with cellular debris in the vitreous³⁻⁷; these changes are consistent with the description of intermediate uveitis.¹⁰

In our series, all patients had signs of severe iridocyclitis in addition to signs of intermediate uveitis. Anterior segment inflammation was characterized by keratic precipitates, posterior synechiae (adhesions of the iris to lens), and cellular reaction in the anterior chamber. All had keratic precipitates that appeared clinically similar to those occurring in ocular manifestations of systemic granulomatous diseases, such as sarcoidosis.

Granulomatous-appearing uveitis has rarely been associated with MS. Recently, Bachman et al¹¹ described five women with granulomatous uveitis and probable MS. The present study confirms and extends their observations, since clinically definite laboratory-supported MS was established in our patients through the use of defined criteria.⁸ In contrast, only one of the cases of Bachman et al¹¹ had clinically definite MS, by their evaluation. No cases fulfilling currently accepted criteria for clinically definite, laboratory-supported disease are presented in their report.^{8,11} A recent histopathological study described granulomatous retinal perivascular infiltrate in MS.¹² The significance of granulomatous-appearing uveitis in MS is uncertain.

Our patients' cases fulfilled the criteria for clinically definite laboratory-supported MS as defined by Poser et al.⁸ Other diseases of the CNS in which uveitis may play a prominent role include Behçet's syndrome, Vogt-Koyanagi-Harada disease, syphilis, tuberculosis, and sarcoidosis.¹³ None of our patients had clinical or laboratory evidence suggestive of Behçet's syndrome, Vogt-Koyanagi-Harada disease, or neurosyphilis. Patient 1 had a positive skin test for tuberculosis, but had recurrent uveitis despite antituberculous therapy. Recently, Sjögren's syndrome has been associated with CNS disease, which may mimic MS¹⁴; in other reports, Sjögren's syndrome has been associated with uveitis.¹⁵ None of our patients had symptoms consistent with Sjögren's syndrome.

Perhaps the disorder most difficult to exclude in our

patients is sarcoidosis. The most common ocular involvement in chronic sarcoidosis is uveitis, which is often anterior and may be granulomatous in appearance.¹⁶ Retinal perivasculitis and vitreous inflammatory debris also occur. Both MS and neurosarcoidosis are protean disorders that may be manifested by diverse involvement of the CNS. Distinguishing between them on a clinical basis may, therefore, be difficult.¹⁷ Similarly, CSF studies including CSF immunoglobulin index and oligoclonal banding are not specific for MS,¹⁸ and, in fact, elevated CSF protein and IgG/albumin ratio and presence of oligoclonal bands may occur in neurosarcoidosis.¹⁹ Furthermore, we recently demonstrated that MR imaging alone can not differentiate MS from sarcoidosis.²⁰

All of our patients were evaluated for sarcoidosis. Chest radiographs showed no evidence of sarcoidosis. They had normal SACE and lysozyme levels and were not anergic. Two underwent limited gallium scanning, which did not suggest sarcoidosis (Cases 1 and 3), and two underwent blind conjunctival biopsies (Cases 1 and 2), which were negative for noncaseating granulomas. Neurosarcoidosis usually affects lower cranial nerves²¹ and only uncommonly the optic nerve.²² Also, patients with neurosarcoidosis usually have other evidence of granulomatous involvement.²¹ We cannot totally exclude the possibility that all these patients had localized parenchymatous neurosarcoidosis. However, this would be highly unlikely given the clinical and laboratory pre-

sentation; MR images also failed to show hypothalamic involvement, hydrocephalus, or discrete nodules, which are the typical CNS findings in neurosarcoidosis.²¹

In summary we report on three patients with granulomatous-appearing anterior uveitis and clinically definite MS. Definite confirmation of this association would be of interest in two respects. First, tissue injury exclusive of CNS myelin is not typical of MS. Further, granulomatous inflammation is not characteristic of the CNS pathology associated with MS. In many cases, granulomatous-appearing uveitis is associated with an underlying granulomatous disease process. Elucidation of the relationship between MS and granulomatous uveitis may indicate how immunogenetic, environmental, or other factors contribute to these putative autoimmune disorders. Second, such anterior uveitis represents a highly treatable manifestation of disease, which should be specifically sought. The significance of the association between MS and anterior uveitis needs further clarification and awaits detailed clinical and neuropathological characterization.

ACKNOWLEDGMENTS

Richard M. Ransohoff, M.D. is supported by the Junior Faculty Award of the National Multiple Sclerosis Society #JF2032-A-1 and by a Clinical Investigator Development Award of the NINCDS #1-K08-NS01265-01.

We gratefully acknowledge Richard A. Rudick, MD and Hershel Goren, MD for reviewing this manuscript and for their helpful comments.

REFERENCES

- Lisak RP. Immunopathogenic mechanisms, abnormal immunoregulation, and immunomodulating therapy in multiple sclerosis. *Clin Aspects Autoimmun* 1987; 1:14-21.
- Matthews WB. Symptoms and signs continued. [In] Matthews WB, Acheson ED, Batchelor JR, Weller RO, eds. *McAlpine's Multiple Sclerosis*. New York, Churchill Livingstone 1985, pp 119-122.
- Archambeau PL, Hollenhorst RW, Rucker CW. Uveitis as a manifestation of multiple sclerosis. *Mayo Clin Proc* 1965; 40:544-551.
- Breger BC, Leopold IH. The incidence of uveitis in multiple sclerosis. *Am J Ophthalmol* 1966; 62:540-545.
- Giles CL. Peripheral uveitis in patients with multiple sclerosis. *Am J Ophthalmol* 1970; 70:17-19.
- Porter R. Uveitis in association with multiple sclerosis. *Br J Ophthalmol* 1972; 56:478-481.
- Bamford CR, Ganley JP, Sibley WA, Laguna JF. Uveitis, perivenous sheathing and multiple sclerosis. *Neurology* 1978; 28(part 2):119-124.
- Poser CM, Paty DW, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Ann Neurol* 1983; 13:227-231.
- Bloch-Michel E, Nussenblatt RB. International Uveitis Study Group recommendations for the evaluation of intraocular inflammatory disease (letter). *Am J Ophthalmol* 1987; 103:234-235.
- Tessler HH. What is intermediate uveitis? *The Uvea*. Yearbook of Ophthalmol, 1985, pp 155-157.
- Bachman DM, Rosenthal AR, Beckingsale AB. Granulomatous uveitis in neurological disease. *Br J Ophthalmol* 1985; 69:192-196.
- Arnold AC, Pepose JS, Hepler RS, Foos RY. Retinal periphlebitis and retinitis in multiple sclerosis. I. Pathologic characteristics. *Ophthalmology* 1984; 91:255-262.
- Haarr M. Uveitis with neurological symptoms. *Acta Neurol Scand* 1962; 38:171-187.
- Alexander EL, Malinow K, Lejewski JE, Jerdan MS, Provost TT, Alexander GE. Primary Sjögren's syndrome with central nervous system disease mimicking multiple sclerosis. *Ann Int Med* 1986; 104:323-330.
- Rosenbaum JT, Bennett RM. Chronic anterior and posterior uveitis and primary Sjogren's syndrome. *Am J Ophthalmol* 1987; 104:346-352.
- Jabs DA, Johns CJ. Ocular involvement in chronic sarcoidosis. *Am J Ophthalmol* 1986; 102:297-301.
- Waxman JS, Sher JH. The spectrum of central nervous system sarcoidosis. A clinical and pathologic study. *Mt Sinai J Med* 1979; 46:309-317.
- Markowitz H, Kokmen E. Neurologic diseases and the cerebrospinal fluid immunoglobulin profile. *Mayo Clin Proc* 1983; 58:273-274.
- Kinnman J, Link H. Intrathecal production of oligoclonal IgM and IgG in CNS sarcoidosis. *Acta Neurol Scand* 1984; 69:97-106.
- Meisler DM, Tomsak RL, Weinstein MR, et al. Magnetic resonance imaging (MRI) and HLA typing in patients with peripheral retinal perivasculitis and intermediate uveitis. *ARVO Abstract*. Invest Ophthalmol Vis Sci, (Suppl.), St. Louis, C.V. Mosby, 1986; 27:121.
- Stem BJ, Krumholz A, Johns C, Scott P, Nissim J. Sarcoidosis and its neurological manifestations. *Arch Neurol* 1985; 42:909-917.
- Rush JA. Retrobulbar optic neuropathy in sarcoidosis. *Ann Ophthalmol* 1980; 12:390-394.