Granulomatous uveitis in neurological disease

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SUMMARY Five women with granulomatous uveitis were diagnosed as having probable multiple sclerosis. Three of the women developed curious iris nodules that resolved with topical prednisolone acetate treatment. The association of granulomatous type uveitis, with or without iris nodules, should alert the ophthalmologist to inquire about neurological symptoms attributable to multiple sclerosis.

The association of multiple sclerosis and granulomatous uveitis was first observed by Wuseke.¹ However, more commonly pars planitis and/or periphlebitis retinae has been emphasised as a common finding in patients with multiple sclerosis.²⁻¹⁸ It is the purpose of this paper to report five patients with probable multiple sclerosis who developed a pars planitis-like picture in addition to curious iris nodules and granulomatous uveitis.

Case reports

CASE 1

A 39-year-old Caucasian woman developed decreased sensation on the right side of her face, transient diplopia, slurred speech, and clumsiness. The cerebrospinal fluid protein was 36 mg/dl (0.36 g/l) with a gammaglobulin concentration of 12.4 mg/dl, =0.124 g/l (normal 8.8, SD 2.6 mg/l, =0.09±0.03 g/l), and 4 white blood cells/mm³. A tuberculin skin test and a test for HLA-B27 were negative. Serum calcium was 9.1 mg/dl, =2.3 mmol/l (normal 8.7-10.2 mg/l, =2.2-2.5 mmol/l); serum B₁₂ was 440 (normal 200-1000) pg/ml (ng/l). A pattern-reversal visual evoked potential showed normal latencies of 119 in the right eye, and 166 ms in the left eye. A brain computerised tomographic scan showed two definite periventricular areas of contrast enhancement on the left side of the cerebral cortex and two more similar questionable areas of contrast enhancement in the left temporal lobe and right occipital horn. These were thought to be most consistent with demyelinating disease. The patient was diagnosed as having multiple sclerosis.

She stated she had noted floaters for five years, and her referring ophthalmologist had treated her for recurrent iritis. Examination of the eyes showed her vision to be 20/40 (6/12) right eye and 20/40 (6/12) left eye. Eye movements were full without evidence of internuclear ophthalmoplegia. Both eyes had 1+ anterior chamber cell and flare and 2+ fine cells in the anterior vitreous. The right macula was oedematous. Both eyes had patchy retinal venous sheathing and inferior vitreous fluffball opacities. There was slight temporal optic nerve pallor, but Goldmann fields were full. Six months later she developed large, lardaceous keratic precipitates and grey-brown, round nodules at the pupillary border of the left eye (Fig. 1). The nodules disappeared on treatment with topical prednisolone acetate 1%, only to recur on cessation of topical steroids.

Fig. 1 Iris nodules at pupillary margin in patient with probable multiple sclerosis.

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CASE 2

A 50-year-old Caucasian woman presented with recurrent iritis. Her neurological problems began at age 18, when she had developed severe right sided headaches, exacerbated by combing her hair, and transient numbness of the right hand and arm. At age 28 she awoke one day with pain and blurred vision in the right eye and diplopia on left gaze. She was not examined by an ophthalmologist, but a neurologist found a left central scotoma and inferotemporal scotoma. There was also mild weakness of the right hand and arm and a decrease in stereognosis. No cerebrospinal fluid protein electrophoresis was done in 1953. A tuberculin skin test was negative. Chest x-ray and pneumoencephalography were normal. A carotid arteriogram was interpreted as showing spasm of cerebral arteries. After the arteriogram she suffered a right hemiparesis and aphasia that resolved over 48 hours, leaving a residual right hemisensory deficit. She was diagnosed as having either multiple sclerosis or an unusual cerebral vasculitis. At age 31 she developed paraesthesias of the left lower extremity and binaural hearing loss. At age 41 she had a hernia of the intervertebral disc between L4 and L5 and underwent laminectomy. At age 48 a right ptosis was noted. Her gait became somewhat broad-based over the next two years.

At age 50 she was referred for ophthalmological examination. Her best corrected visual acuity was RE 20/40-2 (6/12) and LE 20/25 (6/7.5). There was 2+ ciliary flush, large lardaceous keratic precipitates, and 1+ anterior chamber cells in both eyes. There was a posterior synechia in the right eye. The iris of the left eye had a raised brown nodule on the surface of the stroma at 7 00 o'clock. Numerous fluffballs were present in the inferior vitreous of both eyes, but no snowbanking was seen on the pars plana. An HLA-B27 test was positive. However, a rheumatologist thought she probably did not have ankylosing spondylitis. A VDRL was negative. The erythrocyte sedimentation rate was 12 mm/h and serum calcium was 8.9 mg/dl (2.2 mmol/l). Her iritis resolved, and the iris nodule disappeared on topical prednisolone drops. Pseudoexfoliation of the left lens capsule was noted one year later. Six years later she developed sheathing of peripheral retinal venules and bilateral macular oedema.

At age 57 a neurological examination showed proximal leg weakness, normal upper extremity strength, but mild adiadochokinesia of both hands. Deep tendon reflexes were diffusely brisk with bilateral unsustained ankle clonus. There was decreased awareness to pin prick in the right arm and leg, decreased vibration sense in the right ankle, and decreased position sense in all toes. No dysmetria of the arms was present, but this was not tested in the

legs because of the leg weakness. Serum angiotensin converting enzyme was normal at 19 (normal 10–30) units/ml. Her neurologist thought the most likely diagnosis was multiple sclerosis. Other possibilities included an obscure, chronic meningoencephalitis such as Harada's disease, or sarcoidosis, though the latter was very unlikely in view of the normal chest x-ray, serum calcium, and normal angiotensin converting enzyme level.

CASE 3

A 38-year-old Caucasian woman developed a severe headache. One week later she awoke with an uncomfortable pressure sensation in the left orbital area. Later that same day she observed a horizontal black line with a bright line at one end in her left visual field. Over several hours the vision in the left eye became totally grey. An ophthalmological examination several days later showed vision in the right eye to be 20/40 (6/12). With the left eye she could only count fingers at 1 foot (30 cm). There was a left relative afferent pupillary defect. Eye movements were normal. The optic nerve and retina were normal in both eyes. The diagnosis of left retrobulbar neuritis was made, and she was treated with prednisone 60 mg orally for five days. The vision in the left eye gradually improved but did not return to its previous level.

In the ensuing months she noticed difficulty in coordinating her hands, trouble with her balance and gait, and decreased hearing in the left ear. The past medical history showed emotional problems and heavy drinking, for which she had received psychiatric care. Further, she had suffered a closed head injury with loss of consciousness two years previously. Her sister had been diagnosed as having definite multiple sclerosis.

Examination of the eyes six months after the initial episode of decreased vision in the left eye showed best corrected visual acuity of RE 20/20 (6/6) and LE 20/100 (6/30). There was a mild left relative afferent pupillary defect. On colour vision testing in the right eye she missed plates one and four of the HRR (Hardy, Rand, Rittler) pseudoisochromatic plates but arranged the Farnsworth D-15 and Nagel anomaloscope correctly. With the left eye she failed all these tests. The visual field in the right eye was normal. In the left visual field a small central scotoma to the I-4e test object was present. Eye movement testing showed non-smooth pursuit to the patient's left, decreased optokinetic nystagmus with the drum rotating to the patient's left, and poor suppression of the vestibulo-ocular reflex on rotation to her left. Several moderate-sized lardaceous keratic precipitates were present on the corneal endothelium of both eyes. There was an occasional cell in the

Fig. 2a Iris nodules at pupillary border in patient with multiple sclerosis.

anterior chamber in both eyes. Numerous large nodules were present at the pupillary border of the left eye (Fig. 2a). There were many fine, white cells in the anterior vitreous of both eyes. The disc in the right eye was normal. The left disc was pale. There were irregularities of the calibre of peripheral retinal arterioles in the left eye. The iris nodules resolved on topical prednisolone acetate drops.

A neurological examination showed mild left-sided limb dysmetria and bilaterally hypotonic deep tendon reflexes. Laboratory examination showed a cerebrospinal fluid protein of 0.69 g/l, 60 white blood cells/mm³ with 83% lymphocytes, and a cerebrospinal fluid gammaglobulin of 10.2 mg/l (0.1 g/l) (normal 0–0.035 g/l). A chest x-ray was normal. No consistent responses were found with monocular stimulation on visual evoked potential testing. Varying major peaks were present with both eyes stimulated. Auditory evoked and somatosensory potentials were normal. Serum and cerebrospinal fluid VDRL were non-reactive. An electroencephalogram was normal. Computerised tomography of the brain and orbits was normal. Serum protein immunoelectrophoresis showed a raised IgM of 400 (normal 36–266) mg/dl (4 (normal 0.36–2.7 g/l) and normal levels of IgG and IgA. Antinuclear antibodies were less than 1:20 dilution, which is normal. A lupus erythematosus cell preparation was negative. Purified protein derivative (PPD) testing was negative at 48 hours, but tests for trichophyton and mumps were positive. Serum angiotension converting enzyme level was 28 (normal 10–30) units/ml. The white blood cell count was slightly raised at $10.5 \times 10^9/l$, with 5% eosinophils. The patient had HLA-B7 but not HLA-B27. This patient was thought to have multiple sclerosis because of a left retrobulbar neuritis, a left visual pursuit deficit (signifying

Fig. 2b Recurrent iris nodules in association with lardaceous keratic precipitates in same patient.

a left parietal lobe lesion), and a raised cerebrospinal fluid gammaglobulin.

The patient did well on medication until one year later, when she noted decreased vision and a vibrating sensation of the left eye. There was a fibrinous iritis of the left eye with several posterior synechiae and several pupillary iris nodules. Fine vitreous cells and large fluffballs were noted in the inferior vitreous of both eyes. In addition the right eye showed large iris pupillary nodules and lardaceous keratic precipitates (Fig. 2b). Topical prednisolone acetate therapy was started and the iris nodules disappeared. Intravenous fluorescein angiography was normal at that time but eight months later showed bilateral cystoid macular oedema.

CASE 4

A 52-year-old black West Indian nun presented with decreased vision in the left eye. Best corrected visual acuity was RE 20/30 (6/9) and LE light perception. Old pigmented keratic precipitates were present in the right eye but no active uveitis. Virtually confluent lardaceous keratic precipitates covered the whole posterior corneal surface of the left eye. Posterior synechiae were also noted in the left eye. There was mild right optic nerve pallor. The left eye was treated with topical and subconjunctival steroids and mydriatics. Ten days later the right eye developed anterior chamber cells and flare, and topical treatment was started in the right eye. The keratic precipitates slowly resolved over several months. At this time examination of the left optic fundus was possible, showing a pale left optic nerve.

The patient has had several episodes of spastic paraparesis since age 46. She has also had episodes of conjugate lateral gaze palsy, spastic weakness of the right arm, and mild cerebellar ataxia of the arms, more marked on the right. Visual evoked potentials showed a considerably increased latency of the left eye. A neurologist had diagnosed her as having multiple sclerosis. The patient was HLA-B27 negative. Serology tests for syphilis and an auto-antibody screen were negative. X-rays of the skull, chest, and lumbar spine were normal.

CASE 5

A 51-year-old Caucasian woman was referred for ophthalmological examination. Best corrected visual acuity was RE 20/40 (6/12) and LE 20/50 (6/15). Both eyes showed extensive lardaceous keratic precipitates and multiple posterior synechiae. Both optic nerves were pale. The patient was treated with topical steroids and atropine drops, with resolution of the keratic precipitates over three weeks. Mild anterior chamber inflammation persisted for nearly four months.

This patient had developed transient left leg weakness when she was 23. At age 30 she had an episode of retrobulbar neuritis. At 31 she had episodes of urinary incontinence and sensory disturbances of the hands. Later that same year she developed cerebellar ataxia of the upper limbs and right leg, with mild spasticity of all four limbs. This resolved gradually but became aggravated three years later. At age 41 she developed further worsening of her leg weakness. Laboratory studies showed a negative HLA-B27 and negative serology for syphilis and autoantibody screens. Skull, chest, and lumbar spine x-rays were normal. Visual evoked potentials done when she was 53 were normal. A neurologist had diagnosed probable multiple sclerosis.

Discussion

The five reported patients with granulomatous uveitis had a form of clinical multiple sclerosis (Table

1). In all cases the diseases most often associated with granulomatous uveitis (tuberculosis, sarcoidosis, and syphilis) were excluded by appropriate testing. All cases had bilateral uveitis, and cases 1, 2, and 3 had pars planitis and striking iris nodules. In no case did the uveitis appear to coincide with an exacerbation of the neurological condition.

One could suppose that cases 1 to 5 may be afflicted with a disease similar to multiple sclerosis but aetio-logically different from other forms of multiple sclerosis, where the uveal tract remains uninvolved. It is also possible that these patients have some combination of HL-A antigens which predispose them to develop both a uveitis and multiple sclerosis. However rare the coexistence of these two diseases further studies of such patients may help to explain a possible aetiology of multiple sclerosis.

Wuseke first noted the association of multiple sclerosis and uveitis in three patients with peripheral uveitis and multiple sclerosis.¹ Since then numerous authors have reported a similar finding.^{4 7-9 11 14 15 18} Several patients have had pars planitis,^{14 15} while others showed discrete foci of choroiditis.^{4 11} Many patients have been described who have had sheathing of peripheral retinal veins, with or without pars planitis.^{2 3 6 10 12-18} The coexistence of these two inflammatory diseases in the same patient inevitably leads to speculation as to a common aetiology, especially since the plaques of multiple sclerosis have a natural preference for a perivenous distribution. That both retina and brain are neuroectodermally derived lends support to this hypothesis.

Diseases of the central nervous system other than multiple sclerosis which may be associated with uveitis include syphilis, tuberculosis, sarcoidosis, Vogt-Koyanagi-Harada disease, Behçet's syndrome, and toxoplasmosis. We found no evidence for any of these in our patients.

One of Wuseke's patients had iris nodules of the type initially described by Koeppe¹⁹ in patients with tuberculosis. These nodules are found at the inner pupillary margin (Fig. 1). They have also been noted in syphilitic iritis and herpes zoster iritis.²⁰ Our case 2

Table 1 Patients with granulomatous uveitis and neurological disease

Case	Age	Sex	Neurological diagnosis	Eye findings	Comment
1	39	F	Probable multiple sclerosis	Granulomatous anterior uveitis, iris nodules, vitritis, retinal venous sheathing	
2	50	F	Probable multiple sclerosis	Granulomatous anterior uveitis, iris nodules, vitritis, pseudoexfoliation, cystoid macular oedema	HLA-B27+
3	38	F	Multiple sclerosis	Retrobulbar neuritis, granulomatous anterior uveitis, iris nodules, vitritis	Sister with multiple sclerosis but no uveitis
4	52	F	Probable multiple sclerosis	Granulomatous anterior uveitis, retrobulbar neuritis, cystoid macular oedema	
5	52	F	Probable multiple sclerosis	Granulomatous anterior uveitis	

had a nodule on the surface of the iris stroma of the type Busacca²¹ noted in patients with tuberculous lymphadenitis. Since the time of Friedenwald and Friedenwald²² these types of iris nodules have been considered to be a sign of granulomatous uveitis, as they have also been seen in sarcoidosis and sympathetic ophthalmia, two clearly granulomatous diseases.²³ It is intriguing to note that pars planitis as described by Brockhurst *et al.*²⁴ is not associated with iris nodules, though it may present with 'gelatinous' exudates in the anterior chamber angle. In addition lardaceous keratic precipitates are rarely seen in pars planitis.

Our patients showed that pars planitis, traditionally considered a non-granulomatous uveitis, can present with iris nodules and lardaceous keratic precipitates, two clinical signs of granulomatous disease. Admittedly the ultimate differentiation between granulomatous and non-granulomatous disease can be made only histologically. However, in most cases the clinical picture showed should show the differences between the two. Perhaps an altered immune system in the patient with multiple sclerosis may cause granulomatous findings to appear in a disease that is normally non-granulomatous. Nevertheless these patients show that the occurrence of granulomatous uveitis should alert the ophthalmologist to the possibility of multiple sclerosis.

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