Optic neuropathy in sarcoidosis

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SUMMARY Five patients with isolated optic neuropathy and sarcoidosis are discussed. The spectrum of clinical disease was variable but two groups could be identified: patients with chronic progressive visual loss which was associated with thickening of the optic nerve and was refractory to steroid treatment, and patients with acute or subacute optic neuropathy in which the visual loss responded rapidly to steroids. In the latter group steroid dependence developed in all three of the patients. In none did the clinical picture resemble that of the optic neuritis associated with multiple sclerosis.

Sarcoidosis is a multisystem disease in which non caseating epithelioid cell granulomata occur in different sites producing variable clinical features. Ocular involvement occurs in 25% of patients and involvement of the central nervous system has been assessed as occurring in 1–16% of patients. Involvement of the optic nerve is unusual and occurs in only 5% of cases. Clinical manifestations of optic nerve disease in sarcoidosis are diverse and include uveitis or papilloedema but optic neuropathy, granulomata of the optic nerve and optic atrophy secondary to compression by an intracranial sarcoïd mass can occur. Isolated optic nerve disease associated with neither intraocular inflammatory nor extensive disease of the central nervous system is rare. We report five patients with isolated optic nerve disease and sarcoidosis whom we have seen recently at either the National Hospital for Nervous Diseases, Queen Square, and Maida Vale or the Medical Eye Unit, St Thomas' Hospital.

Case 1
A 43-year-old West Indian woman who came from Jamaica in 1962, presented in May 1976 complaining of loss of vision in her right eye. This had occurred five years previously in 1971 when she had noticed sudden loss of vision associated with some discomfort in the globe. Initially vision appeared as a “white fog” but deteriorated over six weeks until she could just count fingers. Vision had remained unchanged until in August 1975, further deterioration occurred with loss of light perception in the right eye though in her left eye vision was normal.

She was admitted to the Maida Vale Hospital in 1976 for assessment. General examination revealed an obese lady with hypertension (BP 180/130 mm Hg). Visual acuity in the left eye was 6/5 with no perception of light in the right. The left visual field was full. There was no pupillary constriction on direct light stimulation of the right eye. There was no proptosis and eye movements were full. Slit lamp examination was normal. The right optic disc was atrophic with hypertensive retinal vascular changes and two small aneurysmal dilatations of the disc vessels (fig 1). The left optic disc was normal. Neurological examination was otherwise normal. Investigation at this time showed a normal blood count, negative WR and an ESR of 30 mm/hour. Radiographs of the abdomen, chest, optic foramina and skull were all normal. CT scan showed normal intracranial and orbital views. It was considered that she had had a right central retinal artery occlusion in 1971 and that there was no clear history of documented progression since that time. She failed to attend for follow up but reappeared in January 1980 when she noticed that colours seemed less bright than usual in her left eye. Although the vision in her left eye continued to deteriorate, she again failed to attend until September 1980 when she was admitted. At that time she complained that her blind right eye had become uncomfortable and itchy. Her general health was good although she rarely took her anti-hypertensive therapy.

On examination the visual acuity in her left eye had deteriorated to perception of light with hand movements in the nasal quadrant. There was 6 mm proptosis of the right eye which was divergent but eye movements were full. The right disc was pale but now swollen and infiltrated with dilatation of superficial capillaries (fig 2). The left optic disc showed temporal pallor. A fluorescein angiogram of the right eye confirmed the extensive dilatation of the capillaries on the optic disc and marked leakage of dye from the disc and surrounding infiltrated retina. Fluorescein angiography of the left eye was normal. Investigation showed a neutrophil leucocytosis of 13,000, ESR 35, raised plasma protein and cerebrospinal fluid (CSF) protein of 69 mg/dl with 19 lymphocytes/mm. Oligoclonal bands were not detected. Hypocycloidal polyclomograms of optic canals and bilateral carotid angiograms were normal but a CT scan showed...
Optic neuropathy in sarcoidosis

thickening of the right optic nerve (fig 3).

A lateral orbitotomy (Mr J Wright) was performed and a cross sectional biopsy of the swollen right optic nerve revealed infiltration with epithelioid and giant cells forming typical non caseating granulomata of sarcoidosis (fig 4). Treatment with Prednisolone 80 mg daily did not produce any visual improvement. Follow up in the subsequent two years showed no further visual deterioration.

Case 2
A 50-year-old West Indian woman who had lived in the United Kingdom since 1963 and had a history of maturity onset diabetes mellitus, presented in February 1982 with progressive, painless visual loss in the right eye. The vision deteriorated over four weeks to no perception of light. She attended her local doctor who could not find any cause for the loss of vision. Four months later she noticed progressive

Fig 1  Case 1. (1976) The right optic disc is atrophic with two small aneurysmal dilatations of the optic disc vessels (left). The left optic disc and retina are normal (right).

Fig 2  Case 1. (1980) The right optic disc is swollen, infiltrated with dilated superficial capillaries (left). The left optic disc is atrophic, with loss of nerve fibres (right).
deterioration of vision in her left eye. She had lost two stone in weight during the previous three months, but otherwise her general health was good. General examination was unremarkable.

Visual acuity in the left eye was 6/36 corrected with no perception of light in the right eye. The left visual field was constricted with an inferior altitudinal defect to a 3 mm white target (fig 5). Colour vision was absent in both eyes. A right relative afferent pupillary defect was present. Slit lamp examination was normal. The right optic disc was atrophic and the left showed some temporal pallor. There was no evidence of diabetic retinopathy. Investigation showed normal blood count, ESR, electrolytes and negative WR. Urinary calcium 8.31 mmol/24 hours (<6.00 mmol/l). Serum angiotensin converting enzyme (SACE) was 74 nmol/min/ml (16–53 nmol/min/ml). CSF protein was 95 mg/dl with 34
white cells/mm\(^3\) (80% lymphocytes, 6% polymorphs). No oligoclonal bands were detected. Chest radiographs showed hilar lymphadenopathy and skull radiographs showed that the right optic foramen was expanded. Orbital CT scan showed thickening of both optic nerves. Pattern reversal visual evoked potentials (VEPs) (Dr AM Halliday) showed absent responses on the right and delay on the left with a latency 161 ms (normal upper limit of latency 115 ms) and an amplitude of 2 \(\mu V\). A Kveim test was positive and Mantoux 1:1000 was negative.

The diagnosis of sarcoidosis was supported by the hilar adenopathy, lymphopenia, raised 24 hour urinary calcium excretion, high SACE levels, and the positive Kveim test. The CSF was compatible. Treatment was started with systemic steroids (80 mg prednisolone daily) and within two weeks the left visual acuity had improved to 6/9 with full colour vision and resolution of the inferior field defect. There was no improvement in the vision of the right eye.

Case 3

A 26-year-old Caucasian woman presented in February 1983 with blurred vision in the left eye progressing over two weeks associated with ocular discomfort on eye movements. She attended the local eye hospital where visual acuity was recorded as 6/60 in the left eye and 6/6 in the right. Fundus

examination was normal. A diagnosis of acute optic neuropathy was made and she was treated with prednisolone 20 mg daily and within two weeks the left visual acuity had improved to 6/12. The steroids were gradually discontinued but three weeks after the last dose the left visual acuity again dropped to 6/60 and the left optic disc was noted to be pale. Two months later she developed pain in both eyes, again exacerbated by ocular movement and visual acuity was now 6/18 on the right and 6/60 on the left. She was treated with prednisolone 40 mg daily and the visual acuity on the right improved to 6/5 but there was no improvement in the left eye. However, the daily dose of prednisolone had to be maintained above 20 mg to prevent deterioration of vision in the right eye. She also complained of episodes of transient tingling in the hands and feet but reported no other neurological symptoms. There was no history of previous joint or skin disease.

General examination revealed a Cushingoid appearance with striae on the legs and abdomen. Visual acuity was 6/6 in

Fig 8  Case 4. Late phase fluorescein angiogram of left eye showing some disc leakage but no macular oedema.
the right and 6/60 in the left eye with a dense temporal and infero-nasal field defect (fig 6). The right visual field was full to a small object. There was a marked left relative afferent pupillary defect. Colour vision was normal in the right eye but absent in the left. Slit lamp examination was normal. The right optic disc showed temporal pallor and the left optic disc was atrophic. Neurological examination was otherwise normal.

Investigation showed a neutrophil leucocytosis of 16,800/mm³ and normal electrolytes and liver function tests. CSF contained 2 WBC/mm³ and protein 34 mg/100 ml with oligoclonal bands. SACE was 18 nmol/min/ml (normal range 16–53). CSF lymphadenopathy and a Kveim test showed non-caseating granulomata. Pattern reversal VEPs (Dr AM Hallday) showed a latency of 122 ms (normal upper limit of latency 115 ms) and amplitude 4.2 μV on the right eye stimulation and no consistent response from the left eye. Somatosensory and auditory evoked potentials were normal. Skull radiographs showed enlargement of the left optic foramen and orbital CT scan no abnormality of the optic nerves.

Case 4
A 32-year-old West Indian man who had lived in the United Kingdom since 1960, presented in December 1979 with a four week history of blurring of central vision in the left eye which had been associated with pain in the eye for three weeks. There were no other neurological symptoms. While awaiting admission he became breathless with a cough and retrosternal soreness and was admitted elsewhere where a clinical diagnosis of pulmonary sarcoidosis was made and a Kveim test performed. His chest symptoms improved spontaneously and he was discharged showed bilateral hilar lymphadenopathy and a Kveim test performed. His chest symptoms improved spontaneously and he was discharged without treatment. However, during the 6 weeks of this illness the vision in the left eye had continued to deteriorate and he lost a stone and a half in weight.

On admission examination showed a thin man without lymphadenopathy or rash. The chest was clear. Visual acuity in the right eye was 6/6 N5 and in the left 6/60, < N48. There was no colour appreciation on the left, and colour vision was normal on the right. There was a left relative afferent pupillary defect. The visual field was full on the right but on the left showed a small dense central scotoma with constricted peripheral field (fig 7). The right fundus was normal but the left disc showed supero-nasal swelling. There was no evidence of retinal vasculitis or uveitis. Fluorescein angiography showed late leakage at the left optic disc without venous leakage or macular oedema (fig 8).

Investigations showed a normal blood count and an ESR of 66 mm in 1 hour. There were detectable immune complexes by polyethylene glycol precipitation at a concentration of 8.8 mg IgG/dl (3.5 ± 1.3 mgIgG/dl). Chest radiographs confirmed the presence of bilateral hilar lymphadenopathy with fine nodular shadowing in the mid zones. The SACE was elevated to about 100 nmol/min/ml. The previously inoculated Kveim test showed non-caseating granulomata. The CSF showed oligoclonal bands but no other abnormality.

The diagnosis of sarcoidosis was made on the basis of the radiological appearances in the chest, the raised SACE and the positive Kveim test. He was treated with a high dose of prednisolone 60 mg daily with rapid improvement in his ocular pain and visual loss. After one week's treatment visual acuity was 6/5 N5 bilaterally with normal fields. Subsequently he has been maintained on prednisolone 10 mg daily. However, whenever the dose has been reduced, he has experienced ocular pain with drop of visual acuity to 6/6 and desaturation of colour, accompanied by breathlessness. At two year follow-up the left optic disc is mildly atrophic.

Case 5
A 31-year-old Caucasian man awoke one morning in December 1981 with loss of vision in the right eye associated with frontal headache and pain on eye movement. A provisional diagnosis of acute optic neuropathy was made elsewhere and he was treated with a short course of systemic steroids with relief of the headache and some improvement in his vision. A week later he developed a polyarthropathy with tenosynovitis of his right hand.

Five years previously he was diagnosed as having acute sarcoidosis when he presented with erythema nodosum, polyarthropathy and bilateral hilar lymphadenopathy. He was not treated with steroids at this time and his symptoms resolved spontaneously. His mother had multiple sclerosis but there was no other relevant family or past medical history.

In January 1982 he was admitted for further investigation following his visual loss. Physical examination revealed an obese normotensive white male with no lymphadenopathy or skin rashes. His chest was clear and his cardiovascular system was normal. He had restricted movements of the small joints of his hands and of his shoulders. There was no abnormality on neurological examination. Visual acuity was reduced on the right to 6/12 N8 with 50% desaturation of a red object. The visual field to the Goldmann I4 isopter was irregularly constricted consistent with numerous arcuate defects and the blind spot was enlarged (fig 9). There was a
Optic neuropathy in sarcoidosis

Clinical features of 5 patients with isolated optic nerve disease and sarcoidosis

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Clinical diagnosis</th>
<th>CSF</th>
<th>Chest radiograph</th>
<th>Optic nerve (CT scan)</th>
<th>SACE nmol/min/ml</th>
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<tr>
<td>1</td>
<td>F</td>
<td>36</td>
<td>Progressive optic neuropathy</td>
<td>19 lymphs</td>
<td>69</td>
<td>Absent</td>
<td>Normal</td>
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<tr>
<td>2</td>
<td>F</td>
<td>50</td>
<td>Progressive optic neuropathy</td>
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<td>74</td>
<td>Absent</td>
<td>Normal</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>30</td>
<td>Acute optic neuropathy</td>
<td>2 lymphs</td>
<td>34</td>
<td>Present</td>
<td>BHL (in past)</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>32</td>
<td>Acute optic neuropathy</td>
<td>11 lymphs</td>
<td>30</td>
<td>Present</td>
<td>BHL Normal</td>
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<tr>
<td>5</td>
<td>M</td>
<td>31</td>
<td>Acute optic neuropathy</td>
<td>19 lymphs</td>
<td>69</td>
<td>Absent</td>
<td>Normal</td>
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SACE = Serum angiotensin converting enzyme.
BHL = Bilateral hilar lymphadenopathy.
Normal values 15–53 nmol/min/ml.

right relative afferent pupillary defect. Ocular movements were normal. The anterior chambers were quiet and there was no vitreous activity. The right optic disc was swollen with haemorrhages and exudates between the disc and macula (fig 10). Examination of the left eye was normal. Fluorescein angiography showed dilated capillaries in the right eye with mild leakage from these in the late phase. There was no leakage at the macula or from the peripheral vessels. The left eye was normal.

Investigations in January 1982 showed haemoglobin 14.8 g/dl white count 3.6 × 10^9/l (54% neutrophils, 34% lymphocytes) ESR 8 mm/hour. Urea and electrolytes, liver function tests, serum and urinary calcium were normal. VDRL, TPHA were negative. Cerebrospinal fluid examination showed an opening pressure of 200 mm CSF and no cells. The protein level was 50 mg/100 ml and no oligoclonal bands were detected. HLA typing was A1, A9, B8 and B17. Radiographs of his chest, skull, hand and spine and an orbital CT scan were normal. Pattern reversal VEPs (Dr Fenwick) showed a latency of 84 ms (normal upper limit of latency 106 ms) and amplitude 7.7 μV on the left and latency 108 ms and amplitude 3.3 μV on the right. He was treated with another course of systemic steroids but there was no further improvement in vision, and the steroids were tailed off after eight weeks. A Mantoux test was positive at 1:1000 dilution and Kveim test showed non caseating granulomata, both performed one month after steroid treatment was finished.

Discussion

We have described five patients with isolated optic nerve disease in association with sarcoidosis. Three patients presented with acute or subacute painful visual loss and the other two with chronic painless visual failure. The diagnosis of sarcoidosis was based on standard clinical criteria. In the first case of progressive visual failure the diagnosis was proved by optic nerve biopsy. Of the three patients presenting with acute or subacute optic neuropathy, one (case 5) had been diagnosed previously as having sarcoidosis and case 4 presented with acute visual loss in association with acute pulmonary symptoms and very high levels of SACE. In case 3 bilateral hilar lymphadenopathy was found at the time of visual loss. Cases 4 and 5 had acute manifestations of sarcoidosis. Our patients showed a spectrum of visual abnormalities ranging from acute reversible visual loss to chronic progressive visual failure. Both manifestations could be seen in different eyes of an individual patient.

Progressive visual failure

In the two patients with chronic failure (cases 1 and 2) the visual loss occurred gradually over a period from four weeks to eight months and was not associated with pain in the affected eye. Both eyes were sequentially affected in each case, progressing to no perception of light in the more severely affected eye. Case 2 developed an inferior altitudinal field defect, but the subsequent rapid response to steroids suggested that the pathogenesis was not primarily vascular.

The appearances of the right optic disc of case 1 are worthy of comment. Initially the disc was atrophic with two vascular prominences in the centre; four years later the disc had become markedly infiltrated with dilated and tortuous vessels. Infiltrated, "cauliflower" optic discs are well documented in sarcoidosis. These optic nerve granulomata commonly occur in association with ocular inflammation. However, if uveitis and other stigmata of sarcoidosis are absent the diagnosis may be confused with that of optic nerve tumours. We have been unable to find a previous report of sarcoïd granulomata developing within an atrophic nerve as in case 1. Case 2 had a thick left optic nerve and may have also had granulomata within it.
Acute or subacute visual loss

The three patients (cases 3, 4, and 5) who presented in this way were initially diagnosed as suffering from acute optic neuritis. However, by the time the patients had been referred for further ophthalmological opinion they had developed unusual features for this diagnosis. Acute optic neuritis of the type associated with multiple sclerosis, often referred to loosely as "demyelinating optic neuritis", is characterized by rapid visual loss, progressing over a week or so, often accompanied by ocular pain increased by eye movement. Examination usually reveals a negative central scotoma, a relative afferent pupillary defect and a normal or mildly swollen optic disc. Spontaneous recovery occurs in 90% of patients often beginning within about two weeks of the visual deficit reaching its peak and continuing for several weeks. Systemic or local (retro-ocular) corticosteroids may shorten the duration of the visual loss but do not alter the ultimate visual prognosis.

Certain features in our patients were atypical for a diagnosis of demyelinating optic neuritis:—1. Although all three patients suffered pain in the affected eye particularly on eye movement, and one (case 5) experienced rapid visual loss, the other two noticed progression of the visual deficit over two to six weeks. 2. Only one patient (case 4) developed the visual field changes of central scotoma with peripheral constriction resembling those of demyelinating optic neuritis. The remaining two patients had more extensive field loss, case 3 showing central scotomata breaking out to involve the periphery and case 5 an irregularly constricted field consistent with multiple arcuate scotomata. These observations contrast with the results of study of 165 patients with demyelinating optic neuritis in which 76% had central field defects with peripheral constriction. The optic discs of our patients varied from atrophy to mild disc swelling confirmed by fluorescein angiography. Case 5 had a deep subretinal haemorrhage on the nasal margin of the right optic disc. Peripapillary haemorrhages in demyelinating optic neuritis are not infrequent though subretinal haemorrhages are extremely rare in our experience.

Investigation Results of visual evoked responses and examination of the cerebrospinal fluid (table) did not serve to distinguish demyelinating optic neuritis from optic neuropathy complicating sarcoidosis. Oligoclonal bands may be found in both and a delayed visual evoked potential is not specific for optic neuritis. An enlarged right optic foramen was found in case 3 but the orbital CT scan did not demonstrate a thick optic nerve in any of these four patients.

Treatment Two patients (cases 3 and 4) showed a good response to corticosteroids. In case 3 the vision improved in both eyes when steroids were given within two weeks of onset of symptoms. However, when treatment was given after the visual deficit in the left eye had been present for more than eight weeks this beneficial effect no longer occurred. In case 4 the vision improved from 6/60 to 6/9 within 24 hours of starting treatment.

The vision of the right eye of case 3 and the left eye of case 4 remained steroid sensitive and reduction of steroids below a certain maintenance dose (20 mg prednisolone daily in case 3, 10 mg prednisolone daily in case 4) resulted in drops in visual acuity and further visual field loss. A persistent dependence of visual function on steroids is rare in demyelinating optic neuritis. The third patient (case 5) showed an initial improvement during the first week on steroids but thereafter the visual deficit remained static.

There is only one other well documented report of acute optic neuropathy resembling demyelinating optic neuritis occurring in the presence of sarcoidosis. Pieron et al described a 23-year-old West Indian woman with hilar lymphadenopathy who presented with rapid visual loss in the right eye accompanied by central scotoma and raised gamma globulin in the cerebrospinal fluid. The visual acuity and visual field returned to normal after twelve days of treatment with prednisolone and synacthen.

Salvesen documented the first case of an acute optic neuritis-like syndrome in a patient with sarcoidosis and chronic lupus pernio but the clinical details are scanty and follow up seven months later showed that vision had improved only from hand movements to 6/36. Similarly, Beardsley et al reported three cases of "retnobular neuritis" in their series of eleven patients. The diagnosis of retinobular neuritis was made because of the normal optic disc and the absence of neurological findings. In each, progressive painless loss of vision occurred over a period ranging from one week to several months. In the latter case spontaneous recovery of vision occurred but the onset was unlike demyelinating optic neuritis. The other two patients improved on steroids.

The mechanisms of visual loss in these patients deserves comment. Progressive visual failure was shown in one case to be associated with involvement of the optic nerve by granulomata and in two others with enlargement of the nerve at CT and/or enlargement of the optic foramen. It seems likely that compression of the optic nerve fibres by sarcoid tissue caused the visual loss in these progressive cases. The mechanism of visual loss in the other cases must be uncertain in the absence of histological data. In the patients who became steroid dependent, it is possible that variations in size of granulomata were determined by changes in dose. It is impossible to exclude the occurrence of a demyelinating optic neuritis of the type associated with multiple sclerosis having devel-
Optic neuropathy in sarcoidosis

Optic neuropathy developed independently of the presence of sarcoidosis in these patients. None of the patients has yet developed other clinical features of multiple sclerosis, but the period of follow-up is too short to conclude that they will not do so.26

The occurrence of irreversible visual loss in several of our patients and the development of steroid dependency in others suggest that these drugs may be needed for patients developing optic neuropathy in a setting of sarcoidosis. Suppressive doses should be used for a short initial period and the dose then reduced fairly rapidly. Long-term steroids should be avoided if possible; if they are required the dose should be kept to the minimum necessary to control the symptoms, and when possible an alternate day regime should be used.

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Optic neuropathy in sarcoidosis.

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