Central nervous system sarcoidosis—diagnosis and management

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Summary

A series of 68 patients with neurosarcoidosis is reported, with particular emphasis on clinical aspects, diagnosis and treatment. A classification system based on clinical diagnostic probability is proposed, consisting of probable and definite disease, the latter being dependent on finding sarcoid granulomas on nervous system histology, which was obtained in 12 patients (18%). The role of investigations, including magnetic resonance imaging (MRI), chest radiography, Kveim skin test, Gallium 67 isotope scanning and cerebrospinal fluid (CSF) studies, is considered. Sixty-two percent of patients presented with nervous system disease, most commonly affecting the optic nerve and chiasm. Other common presentations included cranial nerve palsies, spinal cord and brainstem manifestations. Investigations yielding most diagnostic information included the Kveim test (41/48, 85% positive), raised CSF protein and/or cells (50/62, 81%) and gallium 67 scan (14/31, 45%). Eleven out of 29 patients (38%) patients showed meningeal enhancement on MRI scanning and 43% of scans demonstrated multiple white-matter lesions. Mean follow-up for the group was 4.6 years. Forty-seven patients were seen for >18 months, and over half of these patients progressed despite corticosteroid and other immunosuppressive therapies. The benefit of a large patient database prospectively studied, with extended follow-up is discussed in order to learn more about prognosis and advance therapy in neurosarcoidosis.

Introduction

Sarcoidosis is a multisystem granulomatous disease of unknown aetiology which has a propensity for the lungs, and relatively rarely, the nervous system. Prevalence rates for intrathoracic sarcoidosis vary from greater than 50 per 100 000, for example in New York Blacks, to under 10 per 100 000.[1] Intermediate estimates of 10–20 per 100 000 are likely for Caucasians in London and New York, largely based on results from mass chest radiography. That the disease is frequently asymptomatic is suggested by a Scandinavian study when post-mortems were performed on approximately 60% of all deaths, and histological evidence of sarcoidosis was found in 43 individuals, only three of whom were known to have sarcoidosis during life, yielding a prevalence of 641 per 100 000 at post-mortem.[2] Previous data from large series of patients with sarcoidosis have estimated that approximately 5% of such patients will have clinical involvement of the nervous system,[3–6] although post-mortem studies suggest that ante-mortem diagnosis is only made in 50% with nervous system involvement.[7]

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The criteria upon which a clinical diagnosis of neurosarcoidosis is made have not been firmly established in the absence of positive nervous system histology; considerable variation has existed between series of patients with the disease, although the criteria commonly accepted are a clinical picture compatible with neurosarcoidosis, exclusion of other neurological disease and histological confirmation of disease elsewhere. Newer diagnostic techniques, including magnetic resonance imaging and investigations to exclude other causes of granulomatous diseases must be encompassed in any attempt to refine such criteria further. Not surprisingly, effective means of treating the condition, beyond the use of corticosteroids, have not been established. We report a large number of patients with neurosarcoidosis who have been divided into diagnostic groups according to the certainty with which a diagnosis can be made. The major purpose of this retrospective review of clinical cases was to produce initial diagnostic criteria which could be modified in the future and act as the foundation for a more detailed prospective analysis. This review therefore covers the clinical features, investigations including MRI findings and treatment schedules of what we have defined as 'definite' and 'probable' neurosarcoidosis. Regimens which could form the basis for therapeutic options in the event of troublesome disease are also considered, based on current knowledge, although data for rational, informed decisions are lacking.

Methods

Case notes were examined from patients at the Department of Neurology, Addenbrooke's Hospital, Cambridge and the National Hospital for Neurology and Neurosurgery, Queen Square, London. Computer records at the National Hospital enabled retrieval of data from the 5 years before January 1995. Data from Addenbrooke's Hospital Neurology Department records dated back over 25 years and this information was assessed manually. In total, over 300 patients were identified between the two institutions in whom the diagnosis of neurosarcoidosis had been considered. All of these case notes were then carefully examined, paying particular attention to the conviction with which the diagnosis was made. Investigations were also retrospectively analysed, including all imaging data, biochemical studies on both serum and CSF as well as any histology obtained. Imaging investigations were reviewed as a group.

A total of 68 patients (49 from the National Hospital, 19 from Addenbrooke's Hospital) were found who were considered very likely to have neurosarcoidosis after independent assessment of the case notes by two investigators (JZ and JS). The gold standard for establishing the diagnosis was taken as the presence of positive nervous system histology in the absence of an alternative cause for the patient's clinical condition, and these patients were labelled as having definite neurosarcoidosis. Positive nervous system histology is defined by the presence of sarcoid-type granulomas with epithelioid cells and macrophages in the centre of non-caseating lesions surrounded by lymphocytes, plasma cells and mast cells. There may be a variable fibrotic response, and mycobacteria or other causes for the granulomatous response should not be present.[8,9] Based on our experience of investigating patients with suspected and proven neurosarcoidosis, and our scrutiny of the 68 patients presented in this paper, we propose criteria for the diagnosis of 'definite' and 'probable' neurosarcoidosis, outlined in Table 1.

Particular attention was paid to initial presentation, the presence or absence of systemic disease either prior or subsequent to neurological presentation, investigation findings, length of follow-up and therapeutic measures used to control the disease. An estimate of the overall clinical progression during the follow-up period was made retrospectively by deciding whether the treatment had improved, stabilized, or had little impact on the disease between presentation and most recent clinical review. Only patients followed for a minimum of 18 months were assessed in this fashion.

Data from those patients with biopsy-proven disease in the CNS were also analysed separately to assess whether this group of patients with definite

Table 1 Proposed criteria for the diagnosis of neurosarcoidosis

Definite	Clinical presentation suggestive of neurosarcoidosis with exclusion of other possible diagnoses and the presence of positive nervous system histology
Probable	Clinical syndrome suggestive of neurosarcoidosis with laboratory support for CNS inflammation (elevated levels of CSF protein and/or cells, the presence of oligoclonal bands and/or MRI evidence compatible with neurosarcoidosis) and exclusion of alternative diagnoses together with evidence for systemic sarcoidosis (either through positive histology, including Kveim test, and/or at least two indirect indicators from Gallium scan, chest imaging and serum ACE)
Possible	Clinical presentation suggestive of neurosarcoidosis with exclusion of alternative diagnoses where the above criteria are not met

disease could illuminate the usefulness of particular investigations in other patients with probable disease.

Results

Patient details

Sixty-eight patients were identified as having definite or probable neurosarcoidosis, 49 from the National Hospital and 19 from Addenbrooke's Hospital. Thirty-six (53%) patients were male and 32 (47%) female. Mean age at presentation was 38.9 years (range 21–64 years). Twelve of the 68 (17.7%) had histological confirmation from CNS tissue in the absence of any other identifiable cause, and thus fulfilled the criteria for definite neurosarcoidosis. The average length of follow-up was 4.6 years (range 2 months–18 years). Forty-seven of 68 (69%) patients were followed-up for a period of >18 months.

Clinical presentation

Twenty-six patients (38%) had sarcoidosis previously diagnosed in another organ. Most commonly this was confined to the chest or anterior uvea, but 62% of patients in this series had central nervous system involvement at the time of their initial referral. Details of clinical features when first seen with CNS disease are summarized in Figure 1.

Twenty-six patients (38%) had evidence of optic nerve disease at presentation with CNS disease; 18/26 (69%) had clinical evidence of unilateral and 8/26 (31%) bilateral disease. The characteristic picture was one of an atypical optic neuritis, often subacute in onset, which might recover following steroids or cause permanent visual impairment. Initial steroid sensitivity was occasionally followed by dependence, with symptoms deteriorating below a certain dosage level. Examples of this type of presentation are given in case histories 1 and 2 (Appendix I). Further detailed information concerning visual acuities was available in 16 patients who were followed-up for at least 18 months. Thirteen of these patients had visual acuities of 6/18 or worse in at least one eye at presentation. Over the follow-up period, five patients showed a deterioration to at least 6/60, five patients improved to at least 6/9 and three patients showed no significant change from their presentation acuity. As all these patients received corticosteroid treatment, these data would suggest an approximate 40% chance of appreciable recovery over long-term follow-up with this therapy. The large number of ophthalmological presentations in this series may reflect the links between the National Hospital and a nearby specialist Eye Hospital.

The second most common presenting feature in the series was other cranial nerve palsies in one third of patients. If optic nerve disease is also taken into account, then 72% of patients presented with cranial nerve palsies. The nerves involved are shown in Figure 2. Thirteen patients (19%) had facial nerve paralysis; eight of these were unilateral palsies, two were bilateral and simultaneous, two were recurrent on the same side and there was one case of sequential palsy initially on the left and then involving the right within weeks. Only seven patients who presented with facial nerve palsies were fol-
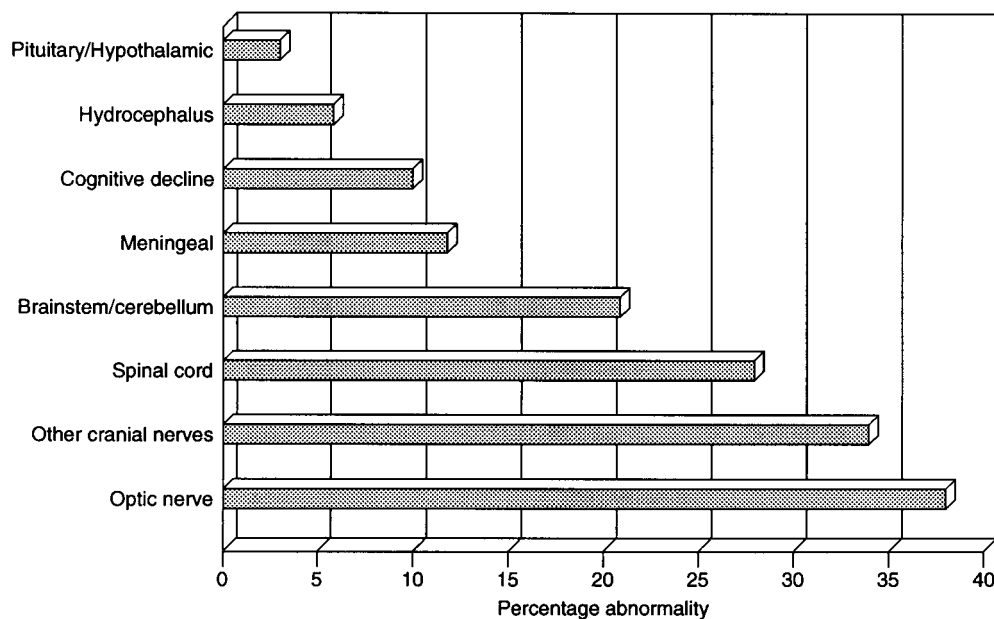

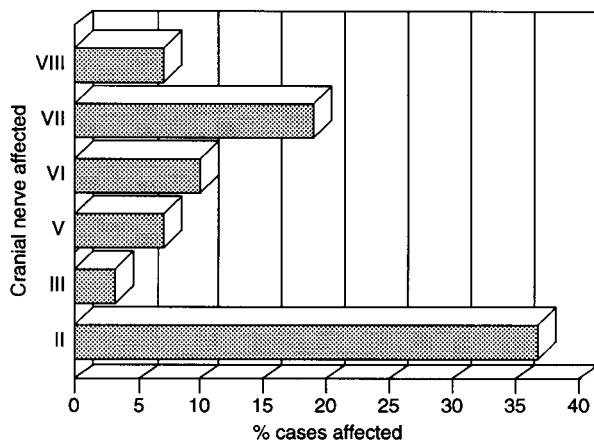**Figure 1.** Clinical presentations of neurosarcoidosis in the 68 patients of the present series.

Figure 2. Cranial nerve involvement in the series total of 68 patients.

lowed up for more than 18 months; five deteriorated or died over this period and two stabilized.

Nineteen patients (28%) exhibited clinical signs of spinal cord disease. In 10 patients this was clinically confined to the cord, while nine patients also had clinical disease elsewhere in the neuraxis (Appendix I, patients 3 and 4). Fifteen cases with spinal cord disease were followed-up for more than 18 months, and 11 of these deteriorated (73%).

Brainstem and/or cerebellar presentations occurred in 14 patients (21%) who principally exhibited limb or gait ataxia and eye movement abnormalities such as failure of vertical gaze. One such presentation is detailed as patient 5. (Appendix I). There was one instance of central vomiting. There were seven examples (10%) of cognitive decline and eight of a meningitic-type illness in the series at CNS presentation.

Investigations

All patients had a chest radiograph at presentation, and 21/68 (31%) were abnormal. The most common abnormality was bilateral hilar lymphadenopathy, seen in 19 patients (28%), four of whom had some pulmonary abnormality in addition. There were two cases of pulmonary shadowing in the absence of obvious lymphadenopathy.

Kveim tests were performed in 48/68 patients (71%), 41 (85%) of which were histologically positive and seven (15%) negative. A single antigen source was used in all the Kveim tests, produced from a spleen removed in 1981. All seven of the Kveim-negative patients were being treated with systemic corticosteroids. One patient had definite disease with a negative Kveim test. This man presented with a convulsion, and was found to have a large contrast enhancing mass in the left temporal region which showed typical non-caseating granulomata on biopsy.

Details of spinal fluid analysis were available in 62 patients. Forty-five (73%) showed elevated protein levels $\geqslant 0.5$ g/l, which did not appear to correlate with clinical phenotype. In 34 samples (55%) there was a raised leucocyte count ($\geqslant 5$ cells/mm^3, range 5–220), which was usually a lymphocytosis. Thus 50 (81%) patients had either an elevation of their age-adjusted CSF protein levels and/or a pleocytosis. CSF glucose analysis was available in 46 patients, 44 of whom had normal levels ($>40\%$ serum level). Two had low glucose: 2.4 mmol/l in CSF against 7.6 mmol/l in serum, and 0.29 mmol/l in CSF against serum concentration of 5 mmol/l. CSF ACE was assessed in 18, and was outside the normal laboratory range for CSF ACE in six. Isoelectric focusing of CSF and serum was available in 54 patients, 20 of whom had evidence for local synthesis (37%), while 10 patients (18.5%) showed serum and CSF oligoclonal bands, indicative of systemic synthesis.

Serum ACE was elevated in 12/51 cases (23.5%). Other biochemical indices were unhelpful in establishing a diagnosis. Serum calcium was normal in all and erythrocyte sedimentation rate was elevated in four patients.

Gallium 67 scanning to look for tracer uptake in salivary and lacrymal glands, chest and spleen was performed in 31 patients, and proved informative in 14 patients (45%).

CT and MRI

MRI or CT scans were available for review in 44 patients, eight of whom fulfilled the proposed criteria for definite neurosarcoidosis. The T2 weighted cranial MRIs of 37 patients (seven definite), were reviewed along with gadolinium-enhanced T1-weighted scans in 29 patients; 11 patients had spinal MRI. Cranial CT was carried out in 20 patients, with contrast enhancement in 15. Seven patients had brain CT without MRI. The results of the MRI review are shown in Figure 3.

The most common abnormality on MRI was multiple white-matter lesions, which were present in 16, 43% of the patients whose scans were reviewed. An example of this is shown in Figure 4 (patient 3, Appendix I). Meningeal enhancement occurred in 11/29 (38%) of those studied and 4/7 (57%) of the 'definite' patients. Figures 5 and 6 (patient 2) illustrate meningeal enhancement. Figure 6 also shows optic nerve enhancement, which was seen in eight patients (28%). Examples of spinal cord involvement are shown in Figures 7 (patient 4) and 8. CT generally produced less information than MRI, particularly in the posterior fossa. Pathological meningeal contrast enhancement occurred on CT in four patients (20%), white-matter lesions were detected in six (30%) and
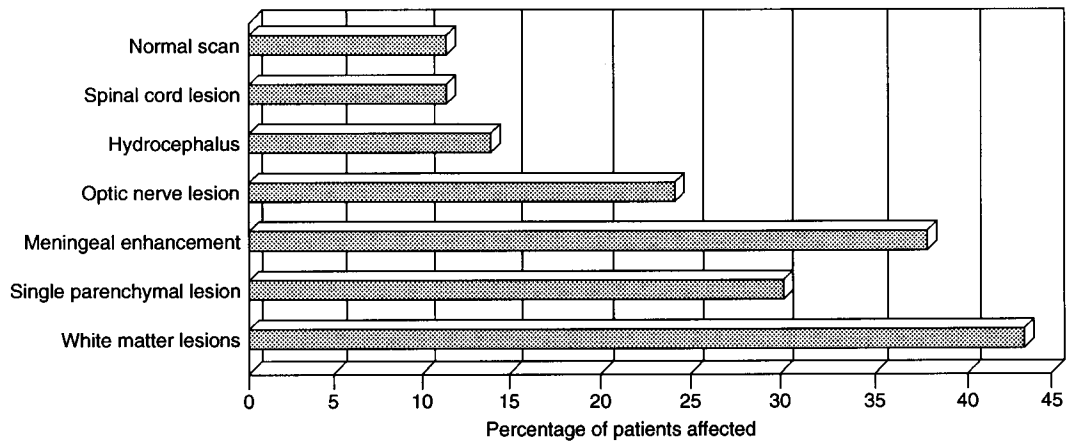
Figure 3. MRI appearances in 37 cases of neurosarcoidosis.

lesions of the optic nerve or chiasm were seen in two (10%).

There were 13 patients who had both CT and MRI and in 11 both investigations were abnormal. In two, cranial CT was normal while MRI was abnormal, implying a greater sensitivity of MRI for detecting lesions consistent with neurosarcoidosis.

'Definite' neurosarcoidosis

Twelve patients fulfilled the criteria for definite neurosarcoidosis. The clinical presentation and investigation results on this group of patients are shown in Table 2. Particular attention was paid to this group of patients in an effort to validate the usefulness of specific investigations. Histological diagnosis was obtained from meningeal biopsy in 6/12 cases, from brain parenchymal biopsy in 3/12, spinal cord biopsy in 2/12 and optic nerve biopsy in one case. The Kveim test was positive in 6/7 patients (compared to 35/41 in the probable cases), an abnormal CSF protein was found in 6/8 (compared to 39/54 in the probable cases) and the cell count was raised in 4/8 (compared to 30/54 in the probable cases). Chest radiography was abnormal in 4/12 patients; gallium 67 scanning was abnormal in 2/3 patients studied. MRI was done in seven definite cases: three of these showed parenchymal involvement, four had meningeal enhancement, three displayed hydrocephalus, two displayed white-matter lesions, and there was one example each of optic nerve and spinal cord involvement.

Treatment and clinical course

We felt that no valid observations could be made concerning the effectiveness of treatment unless patients had been followed-up for at least 18 months. Forty-seven patients meeting this criterion were analysed according to treatment received and overall clinical course. The mainstay of medical treatment in neurosarcoidosis is corticosteroids, and 34 patients received this therapy alone, usually as a combination long-term oral prednisolone with or without intravenous methylprednisolone boluses. Ten (29%) improved or stabilized, whereas 24 (71%) deteriorated. Other therapies were tried only when steroid treatment was becoming ineffective or side-effects were too severe; such treatments included methotrexate, azathioprine and hydroxychloroquine (the latter was taken by two patients in association with methotrexate and corticosteroids). The number of patients treated with any other single regimen was too small to draw firm conclusions. Cyclosporin was used in three instances and was associated with improvement in one case. Cranial irradiation was used in two instances, in one patient after cyclosporin had failed and in another after corticosteroids proved ineffective. Intravenous cyclophosphamide was used at high dosage (400 mg/day until the peripheral white-cell count fell to below 4×10^6/ml) in three patients, who all improved.

Discussion

Diagnosis of neurosarcoidosis

A confident diagnosis of neurosarcoidosis is often difficult, particularly when the clinician is presented with an isolated central nervous system disorder which is likely to have an inflammatory basis. The nervous system is a relatively uncommon site for the disease to manifest and as a consequence, investigation to establish a diagnosis has centred on searching for histological confirmation in other organs. In the present paper we have adopted criteria for making the diagnosis of neurosarcoidosis based upon clinical certainty; thus in order to fulfill conditions for definite disease the patient must have an appropriate clinical syndrome with positive nervous system histology in the absence of any other cause. Probable
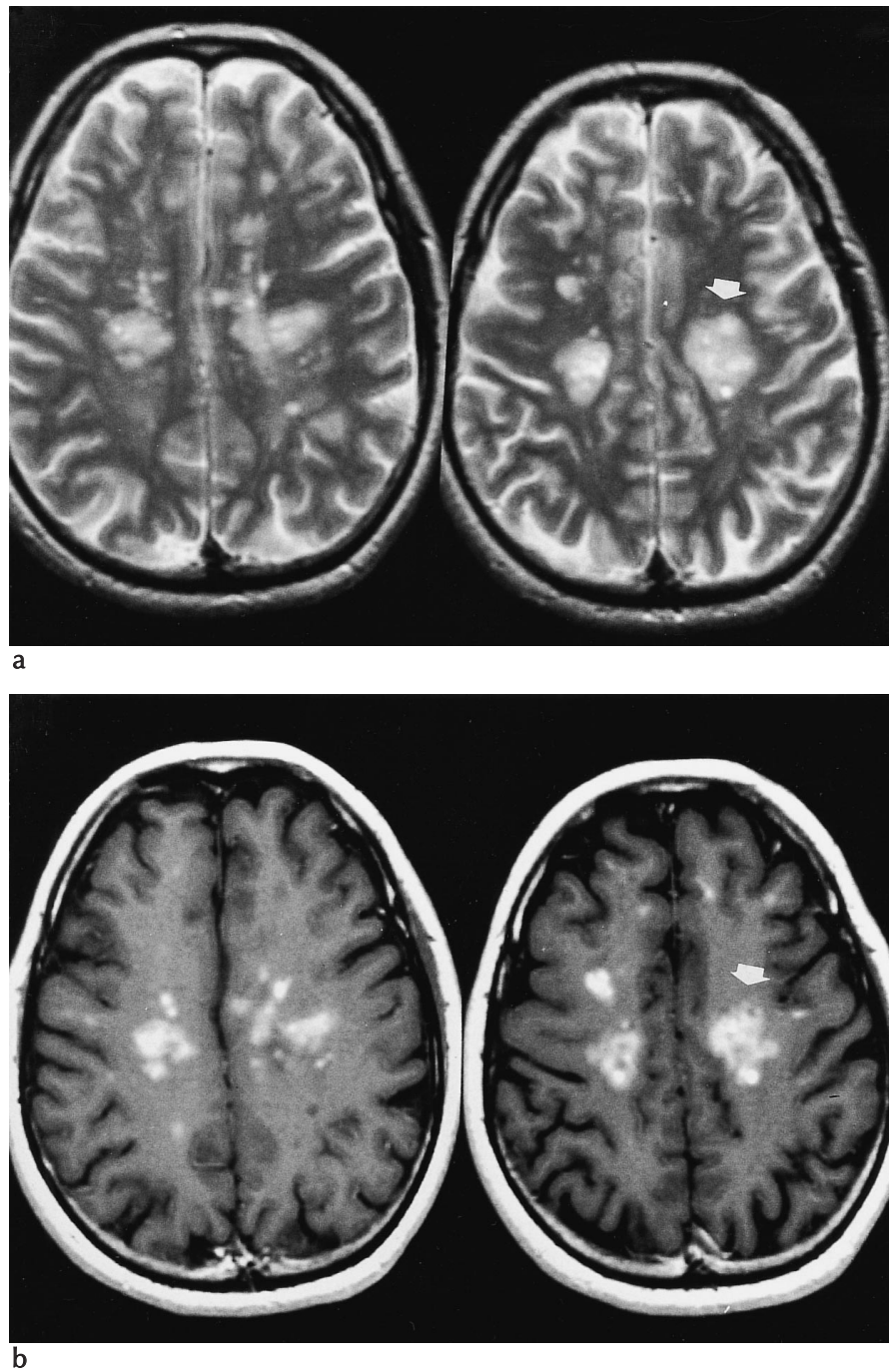
Figure 4. MRI of patient 3: an example of multiple white matter lesions. **a** and **b**, axial T2W and gadolinium-enhanced T1W brain images with multiple, extensive white-matter periventricular and subcortical enhancing lesions, some of which are large (arrowed).

disease has then been defined according to various indirect indicators of disease as outlined in Table 1. These criteria are considerably stricter than in previous series, but we feel a more rigorous definition is necessary for a number of reasons. Most important among these is the possibility of alternative explanations for neurological syndromes in patients with suspected systemic sarcoidosis. Particular difficulty arises with clinical phenotypes resembling multiple

sclerosis with optic nerve, spinal cord or brainstem disease; other diseases may exhibit clinical features similar to those of neurosarcoidosis and these include Lyme disease (with facial nerve palsies and root irritation syndromes), Wegener's granulomatosis (with meningeal involvement), Behcet's disease, meningeal carcinomatosis, tuberculosis and lymphomatosis.

A greater precision in diagnostic definition not only allows for accurate prospective analysis of
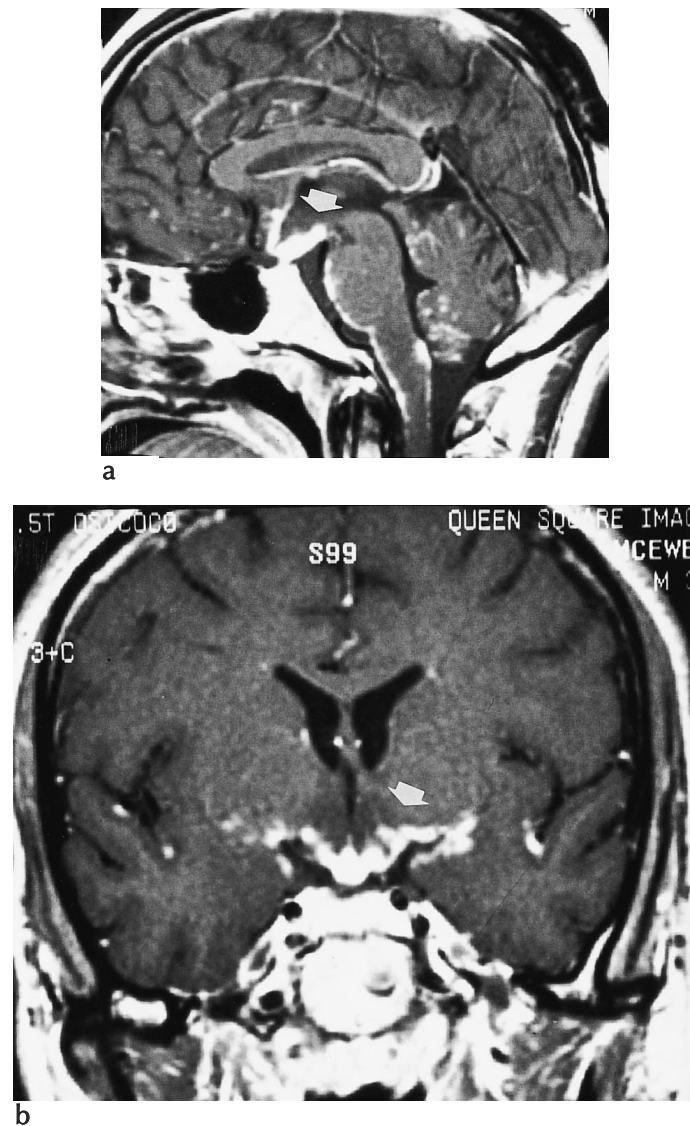
Figure 5. Meningeal involvement in a 32-year-old man who presented with blurred vision in his right eye, with subsequent weight loss, CSF lymphocytosis and protein >2 g/l. **a** and **b** show sagittal and coronal T1W gadolinium-enhanced brain MRI with extensive leptomeningeal enhancement, especially in the basal meninges, and including the optic chiasm (arrowed) and the upper cervical meninges.

prognostic indicators, and better assessment and validation of indirect indicators of disease, but also enables therapeutic trials to be conducted in a meaningful fashion. However, biopsy of CNS tissue is required to make a definite diagnosis of neurosarcoidosis. When the patient is seriously ill with rapidly progressive disease in several parts of the neuraxis, it is important to achieve a diagnosis as quickly as possible in order that appropriate therapy can be commenced, and under these circumstances guided stereotactic or open biopsy is often performed, either of meninges and/or of parenchymal lesions. With less severe disease and/or a more gradual course, it is often more appropriate to perform indirect investigations to look for systemic disease and treat accordingly (see below).

It was hoped that a large number of cases would be obtained which fulfilled the criteria for definite disease, which could then be used as the 'gold standard' to assess the usefulness of any single investigation. However, when assessing such a group, bias is inevitably introduced, as biopsy is undertaken selectively, e.g. on mass lesions, where the possibility of neoplasia has been raised, in patients with severe and rapidly progressive disease or in cases where histology is relatively easy to obtain. The site of lesions (which influences the decision to biopsy) will also influence the clinical presentation—for example, cortical lesions may be more likely to present with epilepsy and be biopsied, thus interpretation of the clinical presentation of this group of patients must be cautious. Another major difficulty with interpreting
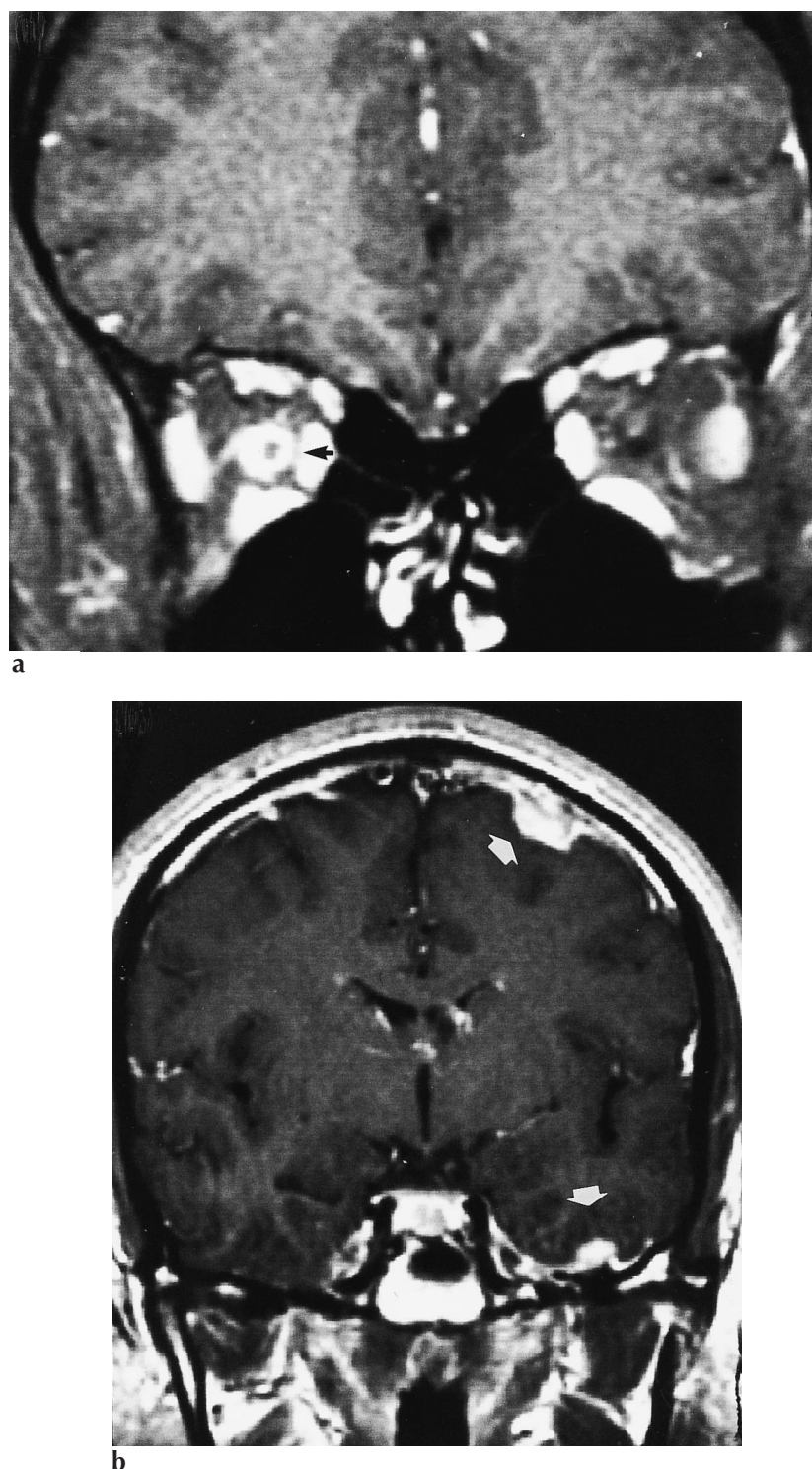
Figure 6. Patient 2. T1W gadolinium-enhanced coronal MRI showing a thickening and enhancement of the dural sheath of the right optic nerve (**a**, arrowed). Widespread dural enhancement with focal thickening of the meninges over the convexity and the left temporal region is also seen (**b**, arrowed).

data from these patients is the incomplete data available, as investigations are often halted once tissue diagnosis is achieved. Notwithstanding these limitations, they do confirm the usefulness of the Kveim test and CSF analysis in the investigation of neurosarcoidosis.

Clinical presentations

In the present series, there was a high prevalence of optic nerve disease at presentation with CNS disease. Although this partly reflects the referral bias of one of the physicians (who jointly attends the Moorfields

Figure 7. Patient 4. T1W gadolinium-enhanced sagittal MRI of the thoracic spinal cord showing focal contrast enhancement and expansion of the cord at T6–T7 level (arrowed).

Eye Hospital and the National Hospital), previous series have confirmed the anterior visual pathways as a site of predilection for neurosarcoid, often second only to the facial nerve. When investigating patients for neurosarcoidosis, a full neuro-ophthalmological workup is indicated, including a search for both anterior and posterior segment disease, with slit-lamp examination and fluorescein angiography, as well as seeking clinical and/or visual evoked potential evidence for optic nerve disease. Unfortunately, optic nerve disease has a tendency to be severe, with profound impairment of visual acuity being all too common. Of the patients who presented with impaired visual acuity and were followed-up for at least 18 months, appreciable recovery occurred in fewer than half.

Facial nerve palsies are a classical manifestation of neurosarcoidosis and have been reported as carrying a good prognosis in previous publications.[5] Although sarcoidosis does not appear to feature prominently among the causes of facial nerve palsies in large series,[10,11] there has not been a large prospective analysis of such patients looking specifically for sarcoidosis. Relatively little comment can be made on the prognosis of neurosarcoidosis presenting with facial palsy based on the current series, in view of the relatively small number of patients in whom long-term follow-up data were available. It was certainly our impression that isolated facial nerve palsies carried a more favourable prognosis than other manifestations of the disease. There may well be a difference in prognosis depending on where the facial nerve is affected along its course. Certainly examples of CSF abnormalities in cases of apparently pure facial palsy in the present series suggest that the lesion may result from a meningitic reaction, but the classical explanation for facial palsy in neurosarcoidosis is that it is secondary to inflammation in the parotid gland, although many early authors also noted the lack of temporal correlation between parotitis and facial palsy.[12] More detailed prospective studies are clearly needed to assess the site and significance of such palsies.

Spinal cord disease was found in 28% of patients at initial neurological presentation. Previous large series have reported prevalence levels of up to 10%.[6,13,14] Syndromes ranged from intramedullary tumour-like presentations to meningitic-radicular syndromes.[15] Fifteen cases of spinal cord disease were followed-up for more than 18 months in the present series and results suggest that such a presentation carries a poorer prognosis than certain other manifestations of neurosarcoidosis as over 70% of the cases deteriorated further during the follow-up period.

Investigation of possible neurosarcoidosis

Establishing the diagnosis of neurosarcoidosis may be difficult, and the only way to acquire firm evidence for the value of any single investigation is to perform a prospective study using appropriate investigations in all patients, especially those in whom a definite histological diagnosis has been obtained. The understandable tendency not to perform further investigations once the diagnosis has been obtained has limited our knowledge on the usefulness of non-invasive methods for investigating
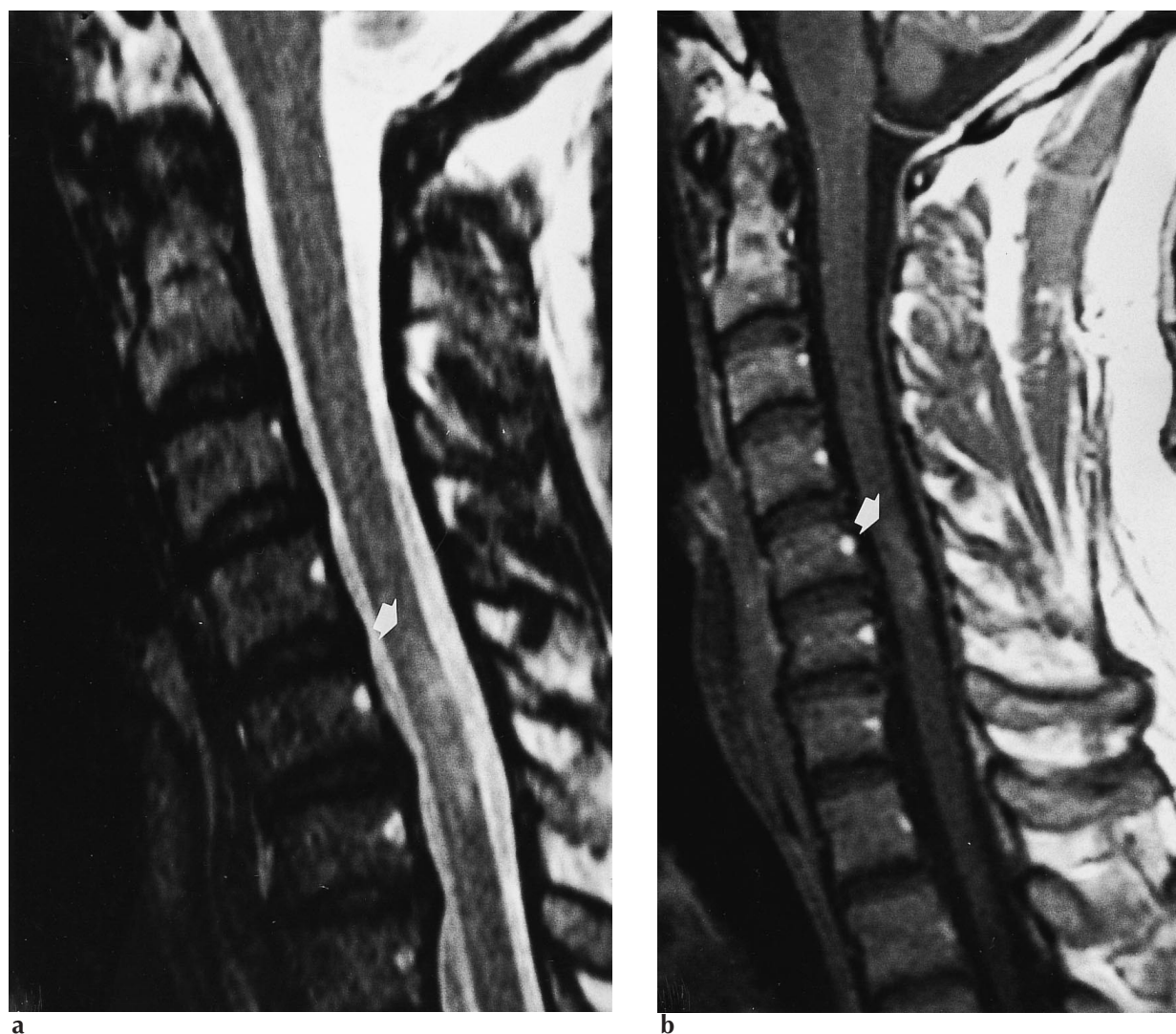
Figure 8. An example of a spinal cord lesion in a 37-year-old man from Sri Lanka who presented with a progressive paraplegia with a positive Kveim test, normal CSF and a positive gallium-67 scan (with uptake in the lacrimal and parotid glands and hilar region. **a** T2W sagittal MRI showing focal area of abnormal high signal at C5–C6. **b** T1W gadolinium-enhanced image shows focal contrast enhancement at that level (same area indicated by an arrow on each image).

neurosarcoidosis. In the present retrospective series, the most useful investigation continues to be the Kveim antigen skin test, which was positive in 85% of patients who were tested. This compares favourably with rates of positivity in other patients with systemic sarcoidosis.[16] The usefulness of this test compared to tissue diagnosis by other means has previously been assessed.[17] That study reviewed the procedures by which histological confirmation was obtained in 79 patients with a final diagnosis of sarcoidosis. Transbronchial lung biopsy was performed in 42, and showed sarcoid-type granulomata in 37. Kveim tests were performed in 44, and were interpreted as being positive in 19 and equivocal in 11. Thus whilst rates of granulomatous 'positive' Kveim test responses are usually lower than those obtained by appropriate tissue biopsy, a positive

Kveim test can be regarded as comparable to that of finding granulomas in a biopsy of a site remote from that principally affected, and compared with other positive tissue biopsies, it has the advantage of an added degree of selectivity for sarcoidosis appropriate to a carefully validated Kveim test suspension. The major problem with the Kveim test lies in the 4–6-week time interval required to elapse before biopsy can be performed. This period may be crucial in intervening in the disease process, particularly when lesions occur in clinically critical sites. Concomitant use of corticosteroids may reduce systemic granuloma formation, including the site of Kveim antigen insertion, and this is a likely explanation for the negative Kveim results observed in the present series, including the case of biopsy-proven disease with a negative Kveim test. All cases with

Table 2 Details of patients with definite neurosarcoidosis

Age (years)	Sex	Initial presentation	Previous disease	Kveim	CSF Protein	OCB	Lymp	Neut	ACE	CXR	SACE	Gal67
31	M	Ep	—	+	2.1	ND	4	–	NS	Par	N	+
55	M	ON, meningeal, Cog	—	ND	1.8	+	37	–	16	N	N	ND
38	M	Ep	BHL, nose*	ND	ND	ND	ND	ND	ND	BHL	N	ND
49	M	SC	—	ND	N	–	2	–	2	N	N	ND
28	M	Ep, Cog	—	–	3.12	ND	90	–	ND	N	N	ND
55	F	ON, Ep, Cog	+	ND	ND	ND	ND	ND	N	N	N	
49	M	SC, Cog	BHL, uveitis	+	1.38	–	<5	–	ND	BHL	Incr.	ND
48	M	ON, VI, unilateral VII	—	+	3.2	ND	20	2	ND	N	N	ND
21	M	ON, VI	—	ND	ND	ND	ND	ND	ND	N	ND	ND
44	F	Unilateral VII, Cog	—	+	4.7	ND	16	–	ND	BHL	ND	ND
54	F	ON	—	ND	N	–	–	–	ND	N	ND	ND
40	F	Ep	—	+	ND	ND	ND	ND	ND	N	ND	+

SC, spinal cord; ON, optic nerve; cranial nerve palsies are depicted in roman numerals, Ep, epilepsy; Cog, cognitive impairment; BHL, bilateral hilar lymphadenopathy; N, normal; ND, not done. Previous disease, evidence of previous clinical manifestations of sarcoidosis. OCB, oligoclonal bands in cerebrospinal fluid; Lymph, lymphocyte count (cells/ml); Neut, neutrophil count (cells/ml); CXR, chest radiology; SACE, serum angiotensin converting enzyme; Gal67, gallium 67 isotope uptake scan; Par, parenchymal lung involvement; Incr, increased.

negative Kveim tests in the present series had received steroids. Hence, although the Kveim test is an invaluable aid in the diagnosis of neurosarcoidosis, up to 3% may be false positive, and negative results may occur with concomitant corticosteroid therapy.

The usefulness of performing 'blind' biopsies from other organs, including liver and lung, in patients with suspected neurosarcoidosis, is uncertain. Three patients in the present series had a liver biopsy although only one patient of the three had abnormal liver enzymes. All biopsies showed sarcoid granulomas in these three patients. While tissue diagnosis from sites outside the nervous system has previously been considered sufficient to establish the diagnosis of neurosarcoidosis in the context of an appropriate clinical syndrome, we would still only consider this as evidence of systemic disease, which by itself is insufficient to be certain of neurological involvement by granulomatous tissue.

CSF abnormalities are common in neurosarcoidosis, and were present in over 80% of cases at presentation. The most common abnormality was an elevation in protein (when 0.5 g/l was taken as the upper limit of normality), sometimes to very high levels, indicative of blood brain barrier dysfunction. Fifty-five percent of patients demonstrated a CSF lymphocytosis, with occasional rare neutrophils and monocytes. Taken together, 50/62 (81%) demonstrated either an elevation of CSF protein levels and/or pleocytosis. Fifty-five percent of patients had CSF oligoclonal bands: one-third of these cases provided evidence for systemic synthesis, and two-thirds fulfilled the criteria for local synthesis. Only three of this latter group of patients had normal CSF protein levels, which may be a way of helping to distinguish them from those patients with multiple sclerosis. These results are in agreement with McLean et al.,[18] who found local synthesis in 36% of cases, but at variance with the results of Borucki et al.,[19] who concluded that local synthesis was an uncommon event. However, neither of these studies had such a large number of patients.

The significance of raised CSF ACE levels in the context of elevated protein concentrations or CSF cell counts remains uncertain. In the present series, these results were abnormal in 33% of cases, a lower level than in previous studies,[20] and perhaps disappointing given the sensitivity of serum ACE for pulmonary sarcoidosis. We believe their usefulness may be principally confined to that small number of patients where levels are raised out of proportion to the protein concentration, when the CSF does not contain large numbers of inflammatory cells and the serum ACE is not elevated. The best estimate would be an ACE index analagous to the IgG index (CSF/serum ACE divided by CSF/serum albumin).

Whole-body gallium scanning remains a useful indicator of systemic disease, which although again is a relatively non-specific measure, adds diagnostic probability to a case. Ga-67 citrate is taken up at sites of active sarcoidosis and also by other inflammatory and malignant diseases, including tuberculosis and lymphomas, but the pattern of uptake among patients with active sarcoidosis is well recognized. Accordingly, as a component of the investigations relevant to the diagnosis of extrathoracic sarcoidosis, it can be very helpful, although con-

strained by the limitations imposed by subjective interpretation. In a consecutive unpublished series of 42 (independent of the present study) such patients, a definite pattern of uptake was obtained in 18 (42%), whilst the pattern of uptake was considered equivocal in eight and negative in 16. In the current series, 45% of patients in whom this investigation was performed proved to have increased uptake, which was usually in the salivary glands or chest. Only three patients had increased uptake in the cranium. Chest radiographs were positive in 30% and were helpful in diagnosis, although not especially sensitive. Chest CT was performed too infrequently in our series to pass comment on, although previous studies suggest it may assist in targeting transbronchial biopsy.

MRI has greatly aided the investigation of patients with inflammatory brain disease and has again proved to be more sensitive than CT in the present series. The range of abnormalities included white-matter lesions, hydrocephalus, mass lesions in the brain parenchyma, meningeal enhancement, enhancement of parenchymal lesions and lesions of the optic nerves and spinal cord, with or without enlargement of these structures. All these abnormalities have been described in previous smaller series.[21–23] The distinction of neurosarcoidosis from MS can sometimes be very difficult. Although none of the appearances are specific for neurosarcoidosis, meningeal enhancement or persistent enhancement (more than a few weeks) of parenchymal lesions are much more suggestive of a granulomatous process, and are not expected in MS. Occasionally, white-matter lesions are seen in sarcoidosis which are indistinguishable from MS.

It is recognized that the diagnostic criteria suggested here will inevitably exclude a number of patients with neurosarcoidosis. However, the further detailed prospective study of patients, so defined, may permit identification of diagnostic factors and patterns which will assist in the diagnosis of milder or atypical forms of the disease.

Treatment and prognosis in neurosarcoidosis

Although this is the largest single series of patients with neurosarcoidosis yet reported, with the most extensive follow-up details, it remains impossible to identify those patients in whom early aggressive immunotherapy would be beneficial. As no prospective data are available in this condition, analysis of the current series and previous publications would suggest that disease presenting in the spinal cord or optic nerve, together with epilepsy, carry a poorer prognosis than facial nerve palsies. Most patients in this and previous series have been treated with systemic corticosteroids, which often carry significant side-effects, as dosages tend to be high and prolonged. Although some patients improve on this treatment, many continue to have troublesome disease, in the present series over 70%. It was particularly noticeable in the present series that symptoms tended to recur at doses of prednisolone less than 20–25 mg/day or the equivalent in other corticosteroid types, making cessation of corticosteroids difficult. The incidence of steroid-related side-effects is extremely high with such prolonged treatment. Concomitant anticonvulsant therapy which induces hepatic microsomal enzymes may reduce prednisolone concentration and efficacy, necessitating even higher oral doses. Bolus pulsed intravenous methylprednisolone gives a high initial loading dose of corticosteroid, and may help to avoid the side-effects associated with long-term oral treatment. We also have the impression that it sometimes modifies the disease, allowing lower doses of oral therapy to be used thereafter.

Even fewer data exist concerning the efficacy of other forms of immunomodulatory therapy. The use of chlorambucil,[24] methotrexate,[25,26] chloroquine,[27] cyclosporin,[28–30] radiotherapy,[31–33] and in this series cyclophosphamide, have all been reported. Our recent experience suggests that methotrexate, usually used weekly at an oral dose of 10 mg, may be of value in maintaining optimal suppression together with i.v./oral prednisolone, and we often use this as a first-line steroid-sparing agent. Hydroxychloroquine has also proved to be a very useful adjunct to steroids, and at a dose of 200 mg/day the Ophthalmological Society has approved its use without recourse to examination with red light. This can be used daily for up to about a year and is worth considering as a first-line agent together with methotrexate. We would consider cyclosporin, cyclophosphamide and fractionated radiotherapy, which all need further assessment. Our current management of neurosarcoidosis usually consists of initiating treatment with 1 g i.v. methylprednisolone for three days together with at least 25 mg oral prednisolone or equivalent per day. Intravenous methylprednisolone (1 g) is then continued on a weekly basis for a number of weeks, allowing a reduction of oral prednisolone to 15–20 mg/day. During this period, oral methotrexate and hydroxychloroquine may be added, especially with severe disease or a poor initial response to steroids. In severe cases, the i.v. methylprednisolone may be continued for some months, with a gradually increasing inter-dose interval. However, it must be emphasized that clear guidelines and indications for treatment together with the drugs which should be used in different clinical circumstances remain matters for further scientific enquiry.

Progress in the management of neurosarcoidosis will require co-operation on a large scale, to establish a large prospective series that could validate the diagnostic criteria postulated in this paper and to enable more trials of treatment. This will enable better data to be obtained concerning the prognosis of clinical presentations, the usefulness of particular investigations, the early diagnosis of neurosarcoidosis, and the development of a rational approach to treatment. At the present time, neurosarcoidosis continues to carry one of the poorer prognoses of any of the protean manifestations of the disease.

Acknowledgements

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Appendix I: Case histories

Patient 1

A 30-year-old office worker born in England of Afro-Caribbean descent noticed that his right pupil was larger than the left in April 1993. He had become aware of light-associated discomfort and redness of the right eye which was subsequently diagnosed as anterior uveitis and treated with steroid eye drops. His symptoms improved within 6 weeks and his eye drops were stopped. Four months later he developed a further subacute deterioration in the vision of his right eye, associated with pain and alteration of colour vision. Examination revealed an acuity of 6/60 on the right and 6/9 on the left, with an inability to identify any Isihara test plates on the affected side. There was a right afferent pupillary defect with bilateral central scotomas and no other neurological signs.

Investigations revealed bilateral hilar lymphadenopathy with reticular-nodular shadowing in both lung fields on conventional radiography and chest CT. Blood investigations revealed normal liver function tests, negative autoantibodies, including anti-neutrophil cytoplasmic antibody (ANCA), but mildly elevated serum ACE at 89 IU/l (52–82 IU/l). Visual evoked responses were unobtainable but pattern reversal electroretinogram was within normal limits bilaterally, suggesting optic nerve disease. CSF showed an elevated protein and pleoocytosis (14 lymphocytes, two neutrophils). MRI showed thickened gadolinium-enhancing meninges over both cerebral hemispheres and marked thickening of the right optic nerve, also with gadolinium enhancement. Transbronchial biopsy at bronchoscopy showed characteristic granulomas, and the patient was commenced on oral prenisolone, 60 mg/day. Over the following year, the visual acuity in the right eye improved back to 6/5 but attempts to reduce the oral prednisolone below 20 mg/day resulted in a recurrence of symptoms. A central scotoma persisted throughout this period, and the patient experienced steroid-related side-effects.

Patient 2

A 54-year-old Caucasian housewife experienced gradual painful visual loss in her left eye over the course of 9 months, associated with a rippling effect in her visual field. At the time there were no associated neurological abnormalities on examination outside the visual system. Temporal artery biopsy was normal, and a course of intravenous methyl prednisolone made no difference to her blindness. The pain became much worse 7 months after the onset, and was exacerbated by adducting the left eye. At that stage there was no perception of light in the left eye and the fundus showed a swollen disc with peri-papillary haemorrhage. Routine blood and CSF investigations were normal, with no oligoclonal bands detectable. MRI showed thickening of the left optic nerve extending from behind the globe to the chiasm with abnormal contrast enhancement. Transection and biopsy of the optic nerve demonstrated non-caseating granulomas with multinucleate giant cells, confirming the diagnosis of optic nerve sarcoidosis. The patient was initially treated with intravenous methyl prednisolone followed by oral prednisolone. Within a year after her operation she was taking 40 mg of prednisolone on alternate days but a slight reduction in the visual acuity combined with a field defect in the right eye necessitated the introduction of azathiaprine 150 mg/day. This was well tolerated, and allowed further reductions in steroid dosage, as spontaneous bone fractures had become a problem. Two and a half years after the introduction of Azathioprine her visual acuity was 6/12 and there was no clinical indication of active disease.

Patient 3

A 27-year-old man of Middle-Eastern extraction developed bilateral anterior uveitis which responded to treatment with steroid eye drops. A year later he developed gradually increasing weakness of his legs with urinary symptoms, impotence and an abdominal sensory level. CSF at the time showed 19 lymphocytes and a protein of 0.7 g/l. Kveim test was positive and myelogram demonstrated an expansion of the thoracic cord. Cranial T2-weighted MRI revealed multiple areas of high signal intensity, predominantly in the white matter, although some also involved the cortex. There was also abnormal high signal on T2-weighted images within the cord at the mid-thoracic level. He was commenced on oral prednisolone after a course of intravenous therapy which improved his leg spasticity somewhat, but attempts to reduce the dose to less than 30 mg/day led to a worsening of his symptoms. His disease slowly progressed over the course of the next 9 years, but clinically appeared to be confined to the spinal cord. MRI 7 years after the onset of his neurological disease again demonstrated numerous areas of high signal within the white matter, many of which were periventricular, and a high proportion of which enhanced with gadolinium. There was also abnormal enhancement of the meninges covering the temporal lobes, but no basal enhancement. On sagittal T2-weighted fast spin echo images, there was an area of high signal of the cord opposite T5 and T6, which had changed little since the original examination.

Patient 4

A previously well 49-year-old Caucasian company director started to experience band-like sensory phenomena around his waist which progressed over the course of 4 months to produce difficulty in walking with sphincter dysfunction. Examination revealed a spastic paraparesis with a sensory level at T8. MRI of the spinal column revealed an expanded spinal cord with pathological contrast enhancement at this site, which was felt to be an intramedullary tumour. A laminectomy was performed and biopsy showed the typical appearances of sarcoidosis. The patient was treated with oral prednisolone and intravenous cyclophosphamide at 400 mg/day until his peripheral leucocyte count fell to below 4×10^6/ml. When last reviewed, over 2 years after the presentation of his illness, he was virtually asymptomatic and able to walk long distances unaided. He was maintained on 25 mg of prednisolone on alternate days together with amytriptyline for residual paraesthesiae.

Patient 5

A 27-year-old Caucasian man developed diplopia, an unsteady gait, left-sided facial weakness and a clumsy right arm over the course of 6 days. Examination revealed upbeat nystagmus in the primary position, a gaze palsy to the left and a right internuclear ophthalmoplegia. Vertical gaze was also reduced. There was sensory loss over the second and third divisions of the trigeminal nerve and a lower motorneurone facial nerve weakness on the left with gait ataxia. CSF analysis showed 7 lymphocytes, a protein of 1.56 g/l and positive Kveim test. MRI revealed a large lesion of high-signal intensity on T2-weighted images in the brainstem which showed pathological contrast enhancement within it. He derived some benefit from intravenous and oral prednisolone so that 2 years later his MRI was normal, but he was left with facial weakness and internuclear ophthalmoplegia.