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A prospective study of 32 patients with neurosarcoidosis

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Abstract. *Background and aim:* There are few published prospective studies of neurosarcoidosis. To establish the incidence of neurological involvement and the response to treatment in patients presenting with sarcoidosis. *Methods:* From 1991 to 1994, 123 patients were studied prospectively at the Prince Charles Hospital using a purpose designed computerised database (1). Consecutive patients were referred for neurological and psychiatric assessment when clinically indicated. Nerve conduction studies were done to confirm the presence of peripheral neuropathy. *Results:* Neurological involvement was identified in 32/123 patients (15 male, 17 female, all white), mean age 48 years, age range 21-80 years. Of the 32 patients, the following frequencies of abnormalities were observed: papilloedema (6%), cranial neuropathy (59%), peripheral neuropathy (47%), mononeuropathy (25%), myopathy (25%), psychiatric disorders (19%), cerebellar ataxia (13%), and hydrocephalus (6%). A neurological improvement was seen in 16/19 (84%) of our patients as a result of therapy, and in 5/13 (38%) who were untreated. Corticosteroid treatment was used in 19/32 patients, with 6/32 requiring pulse intravenous methylprednisolone for initial poor response. The most predictable response incurred in patients with peripheral neuropathy; 12/14 treated patients responding. Only 1/8 patients who remained untreated for this, improved spontaneously. *Conclusion:* Neurological involvement was found more commonly than previously reported (26%). Corticosteroid treatment was found to be effective, although the response was often slow. High dose intravenous methylprednisolone was useful in poor responders (2). Peripheral neuropathy responded predictably to treatment. A formal neurological examination is recommended in all patients with sarcoidosis as neurological involvement may be overlooked. ***(Sarcoidosis Vasc Diffuse Lung Dis 2003; 20: 118-125)***

Key Words. Sarcoidosis. Neurological manifestations. Neurosarcoidosis. Peripheral neuropathy.

Introduction

Neurological involvement with sarcoidosis has previously been reported worldwide in approximately 5% of patients with this condition [3-8]. Retrospective clinical studies have usually found less than 10% of patients with neurological disease, whilst post-mortem series report an incidence of between 15% and 27% [9-11]. Post-mortem results suggest that the true prevalence of neurological sarcoidosis may be far greater than previously recognised clinically. This is supported by electrophysiological evidence from asymptomatic patients [7, 12-16].This is the first prospective study of this size.

A prospective review of patients presenting with sarcoidosis to our Institution was commenced in 1991 to define the prevalence of neurological

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sarcoidosis in an Australian population, and to identify the types and frequency of neurological involvement seen. In addition we aimed to study the efficacy of corticosteroid therapy and other treatments.

Methods

Over a 3.5 year period from July 1991 to December 1994, 123 consecutive patients with sarcoidosis were entered into multidisciplinary sarcoidosis study at the Prince Charles Hospital, Brisbane using specifically designed computerised database. A detailed pro-forma of 250 fields including neurological signs and symptoms was completed by the medical staff on each outpatient visit and after each inpatient stay. Results of investigations and consultations from other sub-specialities (eg cardiology and ophthalmology) were also entered into the database by our data manager. Patients were referred to us for investigation symptoms or abnormal chest radiography.

A minority were seen for an opinion with an established diagnosis of sarcoidosis. At the end of the study period the charts of all patients with suspected neurological involvement were reviewed to confirm the accuracy of our database.

Results

Suspected neurological sarcoidosis was initially identified in 37 patients. Five patients were excluded (2 had syncope from cardiac involvement, 1 headache only, 2 incorrect coding). The remaining 32 out of 123 patients (26%) had a diagnosis of sarcoidosis and neurological disease, which was consistent with sarcoidosis and not explained by another disease process. A neurologist reviewed the majority (78%) of diagnosed cases. All patients had seen the same physician (RKAA) throughout the duration of the study.

There were 15 male and 17 female patients, all white, with a mean average of 48 years at time of diagnosis, ranging from 21 to 80 years.

Table I
Clinical features of 32 patients with neurosarcoidosis presenting between 1991 and 1994

SYMPTOMS OR SIGNS	PATIENTS	PERCENTAGE
Constitutional Symptoms	28	88%
Respiratory	23	72%
Joint	15	47%
Sicca	15	47%
Dermatological	8	25%
Cardiac	4	13%
Uveitis	3	9%

Table II
Chest radiography findings in 32 patients with sarcoidosis at the time of diagnosis of neurological involvement

CXR STAGE		PERCENTAGE
0	normal	9%
I	BHL	44%
II	BHL + P	34%
III	P only	13%

The non-neurologic manifestations are outlined (*Table I*). The majority of patients had constitutional symptoms of fever, lethargy, malaise, night sweats. Clinical evidence of respiratory involvement was also common with 23 patients (72%) having either cough, wheeze, dyspnoea or audible crackles. A chest radiograph was performed on all patients and was normal in only 9% of patients at the time of neurological diagnosis (*Table II*). All patients had either clinical and/or radiographic evidence of intrathoracic sarcoidosis.

A histological diagnosis of sarcoidosis was obtained in 91% of patients (*Table III*). This was obtained by mediastinoscopy in 16/32 patients with a variety of other tissues providing histological evidence of non-caseating granulomata. No tissue diagnosis was obtained in three patients who had negative transbronchial lung biopsies but clinical features highly consistent with sarcoidosis.

Neurological disease was attributable to sarcoidosis in 32 patients (26%) (*Table IV*), the most common abnormality being in the peripheral nerves with 22 patients (69%) having either a peripheral neuropathy, or a mononeuropathy. A "glove and stocking" peripheral neuropathy occurred in 15/32 (47%) and was clinically evident as peripheral sensory loss. Only 1/8 patients who remained untreated for this, improved spontaneously.

Table III
Histological samples obtained from 32 patients with neurological sarcoidosis

SITE	PATIENTS	PERCENTAGE
Mediastinoscopy & Lymph Node	16	50%
Transbronchial	7	22%
Peripheral Lymph Node	4	13%
Skin	4	13%
Open Lung Biopsy	3	9%
Other (liver, bone ,marrow, heart ,pleura, lymph nodes and conjunctiva)	7	22%
Total Positive Tissue Diagnoses	29	91%
Negative Tissue Diagnosis	3	9%

Table IV
Site of involvement of the nervous system in 32 patients with sarcoidosis

NEUROLOGICAL LESION	PATIENTS	PERCENTAGE
Cranial Nerves	19	59%
Peripheral Neuropathy	15	47%
Mononeuropathy	8	25%
Myopathy	8	25%
Psychiatric	6	19%
Cerebellar	4	13%
Hydrocephalus	2	6%
Papilloedema	2	6%
Others	8	25%
Total	32	100%

Mononeuropathy involving the ulnar nerve, lateral cutaneous nerve of the thigh, posterior cutaneous nerve of the forearm, or spinal nerve root was detectable in 8 patients (25%).

Cranial nerve involvement was apparent in 19/32 patients (59%). A total of 32 different nerve abnormalities were observed, including the trigeminal nerve (10 patients, 1 bilateral), the facial nerve (5 patients, 2 bilateral), and the auditory nerve (10 patients).

A progressive, proximal myopathy was noted in 8 patients (25%) in whom it could not be attributed to corticosteroid therapy or other conditions. One patient had tender muscle nodules that resolved spontaneously. Psychiatric depression, cerebellar ataxia, hydrocephalus and papilloedema were also seen. Other conditions included phrenic nerve palsy and vestibular oscillopsia (1 patient each), and carpal tunnel syndrome (5 patients).

Multiple lesions were noted in 22 patients (59%). In 3 patients (9%) the neurological disease was the presenting complaint (one unilateral and two bilateral facial palsies).

Diagnostic investigations were performed on the majority of patients (*Table V*). Nerve conduction studies were the most commonly performed investigation with 35 tests being performed on 18 patients with symptoms suggestive of peripheral nerve lesions. Twelve patients had a total of 29 positive tests, showing most commonly a sensory axonal neuropathy. Multiple tests were done to monitor progression or resolution of their neuropathy. CT brain scans were positive in three patients showing hydrocephalus (2 patients) and a mass lesion (1 patient), which was subsequently not detected on MRI. MRI scans showed periventricular high signal intensity in two patients. In general, MRI with gadolinium enhancement provided superior diagnostic information to CT brain. Five muscle biopsies showed atrophy, non-caseating granulomata and/or denervation. Non-caseating granulomata were found only in two of these biopsies. Sural nerve biopsies were attempted in only five patients, one with histological evidence of granulomata. A diagnosis was made on clinical grounds alone in 13 patients (41%) as 7 had all negative results and no neurological tests were performed on 6 patients.

Table V
Neurological investigations performed on 26 patients with neurosarcoidosis[1]

INVESTIGATION	PATIENTS	POSITIVE RESULTS
CT Head	12	3
MRI Brain	6	2
Muscle Biopsy	7	5
Sural Nerve Biopsy	5	1
Nerve Conduction	18	12
All Tests	26	19

[1] Six patients had no biopsy. "Positive" means consistent with neurosarcoidosis

Corticosteroids were the mainstay of treatment, being given in 19 patients (59%) primarily for neurosarcoidosis. Of these, six patients received intravenous methylprednisolone (1000 mg weekly) followed by oral prednisolone while the others received high dose oral prednisolone (approx. 50 mg daily). Four patients required the addition of methotrexate and one was changed to azathioprine due to suspect, but later disproved, hepatotoxicity. No treatment was given in 13 patients (41%). Both patients with hydrocephalus had no further neurological complications after ventriculoperitoneal shunting. However one patient (male) subsequently required corticosteroids and methotrexate for sarcoidosis involving his lungs and later developed cutaneous cryptococcosis. He is still under review by the first author.

Complications were noted in 8/19 patients (42%) treated with corticosteroids. Four developed significant cushingoid features, two developed impaired glucose tolerance, one patient developed rib fractures and one mood disturbance. Four patients developed significant infectious complications. Two required hospital admission for severe bacterial pneumonia, one developed cryptococcal pneumonia, and one *E. coli* sepsis.

Table VI
The response in 19 patients with cranial nerve lesions in 32 patients with neurological sarcoidosis[2]

	ALL PATIENTS	TREATMENT (Rx)	NO Rx
Resolved completely	8	6	2
Improved	7	7	0
Unchanged	4	2	2

[2]The response to treatment was not significantly different between the treated and untreated groups (p= 0.138)

All patients but one survived to the date of review, with an average follow-up of 29 months (1-164 months). One patient died from cardiac sarcoidosis. Six patients (19%) had complete resolution of all symptoms; fourteen (44%) had partial improvement, while eleven (34%) patients had no change in their signs or symptoms. An improvement was seen in 16/19 (84%) of our patients as a result of therapy, and in 5/13 (38%) who were untreated. The response to therapy for individual regions of the nervous system is outlined (*Table VI* and *VII*).

Table VII
Peripheral Nerve. The response in 22 patients with peripheral nerve lesions[3]

	ALL PATIENTS	TREATMENT (Rx)	NO Rx
Resolved completely	1	1	0
Improved	12	11	1
Unchanged	9	2	7

[3]There was a significant difference in response rate between the treated and untreated groups (p = 0.003)

Discussion

No part of the nervous system is immune from potential involvement by sarcoidosis, and its manifestations may go unrecognised for long periods of time. However, it has a predilection for specific regions of the nervous system, especially certain cranial nerves, the peripheral nerves, and muscles.

Although cranial nerve involvement is the most frequently reported manifestation, in our study it occurred in 59%, which is comparable to that of other studies, albeit retrospective. Facial nerve involvement is described commonly. It is of lower motor neurone type, and due to the proximal nature of the lesions, is classically associated with loss of taste on the anterior 2/3 of the tongue and hyperacusis. Mastoid pain is also a common feature, and the facial palsy usually resolves spontaneously. Bilateral involvement occurs in around one third of patients. Other cranial nerves have been reported less frequently, including CN V (facial sensory loss), CN VIII (sensorineural deafness), CN II (optic neuritis, optic atrophy or papilloedema), and CN IX (diminished gag and palatal sensation). These may be the only signs and, as they may be subtle, they are often difficult to diagnose.

The incidence of cranial nerve involvement in our group did not differ significantly from most major studies (*Table VIII*). Sensory involvement (CN V and CN VIII) was more common than reported and often left a permanent deficit. CN II involvement was transient and spontaneous resolution was observed in most.

Our most surprising finding was the high incidence of peripheral nervous system involvement (69%). This included both the peripheral mononeuropathy and the symmetrical peripheral neuropathies. Earlier reports regarded mononeuropathies as the more common defect [17,18]. However more recent studies have found a pre-

Table VIII
Published series of neurological sarcoidosis over the past 20 years

	CURRENT STUDY AUSTRALIA 1996 PROSPECTIVE	CHEN [4, 5] AUSTRALIA 1992 RETROSPECTIVE	CHAPELON [3] FRANCE 1990 RETROSPECTIVE	OKSANEN [7] FINLAND 1986 RETROSPECTIVE	STERN [8] USA 1985 RETROSPECTIVE	DELANEY USA 1977 RETROSPECTIVE
Total patients	123	335	n/a	n/a	649	77
% Any Neurological	26%	4.5%	% not stated (35 patients studied)	% not stated (50 patients studied)	5%	10%
% Cranial nerve	59%	47%	37%	42%	73%	61%
% Any peripheral nerve	69%	7%	40%	18%	6%	9%
% Myopathy	25%	27%	23%	10%	12%	9%

ponderance of peripheral neuropathies [3-8,19]. Although we concur with the more recent data, our incidence of symmetrical polyneuropathies far exceeds that reported in the literature (*Table VIII*). We believe this is due to our performing a thorough neurological examination in all patients presenting with sarcoidosis as part of our prospective study protocol. Whenever symptoms occurred that might have suggested neurological disease, a neurological referral was sought. It also reflects the deficiencies of retrospective trials. A retrospective review of charts of patients with sarcoidosis at our institution revealed similar deficiencies, with only small proportion of patients found to have neurological involvement. Most had not had a detailed neurological or ophthalmological examination. The relatively high incidence of carpal tunnel syndrome reported prospectively by one sarcoid clinic was not found in our study where a detailed neurological examination was done on every patient who also saw a neurologist [20]. Although some mild cases may have been overlooked, the clinical significance of mild carpal tunnel compression of the median nerve which is detectable only on nerve conduction studies is debatable.

Muscle involvement has been reported on biopsies in up to 86% of asymptomatic patients, particularly those with an acute onset of their disease and erythema nodosum reflecting the systemic nature of sarcoidosis [21,22]. Symptomatic involvement usually occurs with a slowly progressive proximal myopathy. This was present in 8/32 (25%) of our patients, which is consistent with previous reports [3-8,19]. Acute myositis and rarely a nodular myositis can occur and can be easily identifiable on MRI in our experience and distal muscle atrophy has been described secondary to sarcoid neuropathy.

We also found psychiatric depression, dementia, hydrocephalus, and cerebellar ataxia attributable to sarcoidosis. Other conditions that have been described include encephalitis, space occupying lesions, seizures, hypothalamic and pituitary disease, spinal cord lesions, and Guillain-Barré syndrome [3-8,22] We did not however observe any of these abnormalities during this study but have subsequently seen a patient with diabetes insipidus from sarcoidosis.

When compared to the published series in the last twenty years (*Table VIII*), the incidence of cranial nerve and muscle involvement was comparable to that reported. However our incidence of peripheral nerve involvement was far greater (69% compared with 6-40%). This has been attributed to our greater detection of more subtle peripheral neuropathies. The majority of these patients were reviewed by a neurologist to confirm the presence of disease and to formally exclude other possible causes. Patients with confounding conditions, the commonest being diabetes mellitus, were not included in this group.

Despite a wide range of investigations being performed on our patients, they were often non-diagnostic. CT head scans are reported to be abnormal in less than 50% of patients with central nervous system disease. MRI brain scans are more sensitive showing periventricular white matter high signal intensity of T2 weighed images, leptomeningeal enhancement with gadolinium, or other abnormality in about 80% of patients [7,8, 12,23-25]. Our results were similar to these.

Although biopsy of neural tissue was obtained in a minority of patients with neurosarcoidosis, non-neurological biopsies, especially of lung and mediastinal lymph node proved the most frequent way with which to establish the diagnosis histologically. The Kveim test has not been available in Australia for many decades. However when available it may prove of value if biopsy tissue is difficult to obtain especially in the frail or elderly. The lack of radiological evidence of pulmonary sarcoidosis does not preclude a positive transbronchial lung biopsy, which if done by an experienced bronchoscopist, has a very low morbidity and mortality.

Although muscle biopsies may show non-caseating granulomata, more common findings are atrophy and changes of denervation. Indeed this was the predominant finding in this study. Expertise is required both by the surgeon and the histopathologist in obtaining adequate biopsy material from muscle. In this study, only one histopathologist who has specialised in muscle pathology was routinely consulted for this purpose. MRI may also prove useful in diagnosis of sarcoidosis involving muscle. Sural nerve biopsies may reveal granulomata but in our experience may

cause significant residual local pain and numbness, and cannot be repeated to follow progress. Occasionally biopsies of intracranial mass lesions are often advisable in our experience to differentiate sarcoidosis from other conditions including neoplasms, nocardiosis and cryptococcosis. An initial response to corticosteroids without a prior biopsy may lead to a false sense of security. One patient subsequent to this series has since developed pulmonary cryptococcosis and intracerebral nocardiosis while on corticosteroids, both biopsy-proven. For the diagnosis of cerebral nocardiosis, brain tissue is required as there is no serological test available as occurs with cryptococcosis. However in areas of the brain, which are difficult to biopsy, circumstantial evidence, a response to corticosteroids and regular review may be the only option.

In central nervous system sarcoidosis, cerebrospinal fluid examination may show a leucocytosis, elevated protein and reduced glucose, all non-specific findings. The CSF has been reported to be normal in 30% of such cases. Elevated ACE in the CSF may occur in 59% of cases due to local production in the CNS. This finding is again non-specific, occurring in a number of CNS malignancies, vasculitides and infections. The assay which is more sensitive that that used for serum ACE is usually done only in specialised centres and suffers from lack of sensitivity. Although it has its enthusiasts, in our experience it is neither a cost-effective investigation, nor one of any clinically useful diagnostic value [26]. This opinion is not from want of interest in angiotensin-converting enzyme which has been the subject of considerable investigation by the first author [27-31]. It should be remembered that the choroid plexus is rich in ACE [31]. Until further studies of CSF-ACE prove it a sensitive test, it may be relegated to the annals of the history of sarcoidosis like its non-diagnostic cousin, ACE in bronchoalveolar lavage fluid [30]. Lysozyme and _2 microglobulin have also been studied and, although they are often elevated, there is no correlation with CSF ACE. Intrathecal immunoglobulin synthesis is detected in up to 1/3 of cases, and the CSF CD 4:8 ratio is elevated as is seen in the peripheral blood and lung lavage of sarcoidosis patients [7,12,32-34].

Nerve conduction studies are useful diagnostic tests as they may confirm the presence of a peripheral nerve lesion when symptoms are present but signs are not able to be elicited. Serial testing is helpful in confirming a response to treatment. An axonal neuropathy is the most common finding. In our series, this test had the greatest yield of positive results when performed on symptomatic patients. Other neurophysiologic investigations that may be performed include visual evoked responses (VERs) and brain-stem auditory evoked potential (BAEPs).

These have been reported as being abnormal in up to 61% and 42% of patients with neurological sarcoidosis respectively. Visual evoked responses performed on patients with sarcoidosis have been reported to be abnormal in 24%, in the absence of neurological symptoms [7,12-16]. This helps confirm our opinion that neurological involvement is more widespread and more common than has been recognised.

Oral corticosteroids are the mainstay of treatment of neurological sarcoidosis. Their use has been advocated in most patients with neurological sarcoidosis and response rates have been quoted as up to 92% compared with 35% improvement in untreated patients [3,7,8,35]. Intravenous pulse methylprednisolone has been used where there is no response to oral agents, or where side-effects are intolerable [2]. An improvement was seen in 16/19 (84%) of our patients as a result of therapy, and in 5/13 (38%) who were untreated. When individual neurological lesions are considered, the cranial nerve abnormalities have the best prognosis. Specific conditions such as papillitis were particularly responsive, and progressive peripheral neuropathies also improved with corticosteroid therapy. Although our population was small and despite some possible selection bias, those who received corticosteroids for peripheral neuropathies had a statistically significant clinical improvement compared to those who remained untreated.

Alternative drug therapy may be indicated in patients where corticosteroid side- effects are intolerable, or where the response is sub-optimal. The first author has used methotrexate extensively in sarcoidosis, both neurological and non-neurological. It is efficacious and well tolerated by the majority of patients, as a steroid-sparing agent and less commonly as a single agent. Why cutaneous sarcoid responds exceptionally well to methotrex-

ate as a single agent in comparison to the more variable response in neurosarcoidosis is unknown. Azathioprine is a more toxic drug than methotrexate, and with the harsh Australia sun, is associated with a high incidence of skin cancers which may be significant limitation in some patients.

A recent review of combination therapy for sarcoidosis by, and not confined to neurosarcoidosis, concluded that the use of other combinations of immunosuppressant therapy, such as methotrexate and azathioprine, has been disappointing mainly because of side-effects such as liver toxicity, opportunistic infections and malignancy [36]. Methotrexate, azathioprine or chlorambucil (in increasing order of toxicity) alone or in some cases with corticosteroids, as a general rule are better tolerated than two of these agents together [37-39]. Cyclosporin use has met with disappointing results [36,40]. Thalidomide has not been approved for use in neurosarcoidosis in Australia and there have been no published controlled trails of its efficacy. Although used widely for in rheumatoid arthritis, leflunomide has not been authorised for use in sarcoidosis in Australia. However has been used anecdotally with methotrexate in patients with severe ocular sarcoidosis [36]. Cranial radiotherapy has been used successfully for non-responsive central nervous system disease [40-42]. Surgical intervention may be required for hydrocephalus, but is otherwise rarely necessary.

Conclusions

Involvement of the nervous system by sarcoidosis is more common than previously recognised. This has been alluded to by a number of studies, including post-mortem series [9-11] and electrophysiological studies [7, 12-16] and is confirmed by our prospective clinical study. In general central nervous system involvement appears well-recognised possibly as it is more obvious clinically, in contrast to the peripheral nervous system which is often overlooked [43]. Corticosteroids remain the major therapeutic option although there are as yet no controlled trials to support their efficacy. Our data suggest that there is a significant benefit from corticosteroids in patients with peripheral neuropathies. For the majority of cases of neurosarcoidosis, biopsy of neural tissue has a low yield and ultimately a clinical diagnosis had to be relied on in most cases after the reasonable exclusion of other causes, and where possible, the biopsy of non-neural tissues. A recent review of this subject reveals the dearth of prospective studies and controlled treatment trials of neurosarcoidosis and our scientific shortcomings with regards this condition [44]. Further studies are clearly needed.

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