Sarcoidosis of the central nervous system:

safety and efficacy of treatment, and experience of biological therapies

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All patients consented to their clinical details being reported and the work has been conducted in compliance with the declaration of Helsinki.

Abstract

Background: Neurological complications of sarcoidosis are uncommon and the natural history and optimal treatments under-researched. With the advent of biological therapies, it is important to define the clinical characteristics and immunopathology of the disease.

Methods: Patients referred to and treated within the Centre for Neurosarcoidosis over a 15 year period who had biopsy proven “highly probable” disease of the central nervous system were studied prospectively.

Results: Corticosteroids were used effectively in all patients, immunosuppression in 79% and TNFα antagonists in 23%. Treatment with steroids alone inevitably led to relapse, and low dose immunosuppression was ineffective in those with severe forms of the disease. Use of biological therapies substantially improved outcome.

Patients with cranial neuropathy had an excellent outcome. Those with pachymeningitis had marked radiological abnormalities but less disablement. Those with leptomeningitis had an invasive, destructive disease which responded well to treatment but with residual neurological impairments. Treatment was required for many years, but the risk of relapse following treatment withdrawal was low. Infective complications arose in six. There were two deaths, neither directly related to the neurological disease nor its treatment.

Conclusions: This prospective study of the natural history and treatment response in neurosarcoidosis provides evidence that the use of high dose immunosuppression and early and prolonged use of biological therapies is associated with greatly improved outcomes and lower mortality. The data may be used to plan further studies and treatment trials, and provide class IV evidence for the effectiveness of biological agents in the treatment of Neurosarcoidosis.

**Introduction**

The natural history of neurosarcoidosis has not been studied comprehensively, nor have guidelines for the treatment of the disease been formulated. There is an accumulating evidence base, and a few clinical trials, of treatment of the systemic disease[1], and, correctly, the same treatments have been tried in the neurological form; there are case reports and small series but no randomised controlled trials. With the advent of specific biological agents, which appear to have great effectiveness in the treatment of inflammatory diseases including sarcoidosis, it is important to define what the role of these treatments is in neurosarcoidosis.

The clinical characteristics, imaging features and CSF results have been described in a cohort of 166 patients treated prospectively in the Centre for Neurosarcoidosis; one third had cranial neuropathies of whom over half had abnormal brain imaging and CSF, and two thirds had involvement of the brain and / or spinal cord, all of whom had clear imaging abnormalities; there were clear differences between those with pachymeningitis and leptomeningitis, and in each group abnormality of CSF correlated with disease severity [2]. This paper describes the natural history and response to treatment in the same cohort and uses the results to discuss optimum treatment.

**Methods**

The Centre for Neurosarcoidosis is a national referral centre for the investigation and treatment of the disease. The investigation results are reviewed (including the pathology when available) and further investigation made if necessary. Those in whom after investigation a diagnosis of systemic sarcoidosis with pathological support was agreed, in whom the neurological features and investigation results were considered to be in keeping with a neurological complication of the systemic disease, have been included in this prospective study. All patients therefore were considered to have a “highly probable” diagnosis of neurosarcoidosis according to the World Association of Sarcoidosis and other Granulomatous diseases (WASOG) sarcoidosis organ assessment instrument [3]. In addition, patients with an isolated form of the disease in whom the neuropathological features were considered to be typical for the disease were included. An assessment of disablement was measured in each case before and after treatment using the modified Rankin score (MRS) [4].

The study was undertaken prospectively following permission from the local research ethics committee, and all patients gave informed consent to participate. Data were obtained in a prospective fashion, but not using a uniform treatment protocol with a defined set of hypotheses and outcomes to be measured. Patients were treated individually and treatment pathways were not dictated by the study but by clinical need. The study period was 2001 – 2016. Use of TNFα antagonists in the centre commenced in 2003.

Statistical analysis: group comparisons were made using Fisher’s exact test and the Mann-Whitney U test, correlations using Spearman’s rank correlation test. Analyses were performed with Minitab software, version 17, and multiple regression analysis using the Excel data analysis add-in.

Data not published within the article are available in a repository in the centre for Neurosarcoidosis and these anonymized data are available to be shared upon request by a qualified investigator.

**Results**

The systemic features, patient demographics, imaging, blood and CSF investigations results are provided in the companion paper [2].

*Cranial neuropathy*

1. facial neuropathy (26 cases): a full recovery occurred in 20; all bar one of the 14 unilateral cases, and in five of the 12 bilateral cases there was little or no recovery (p = 0.06). Those with isolated facial neuropathies were treated with steroids alone unless the systemic disease required greater treatment.

2. There were 12 cases in which multiple adjacent cranial neuropathies arose: these patients were also treated at the outset with steroids alone; a full recovery occurred in those with sixth and seventh neuropathies, a recovery occurred in one and a partial recovery in one with abnormal imaging in those with fifth, sixth and seventh neuropathies. Those with involvement of the vestibulocochlear nerve required treatment with steroids and immunosuppression, and neither recovered completely.

The presence of an imaging or CSF abnormality was not associated with a failure of recovery (p = 0.6 and p = 0.5 respectively).

Each of those with lower cranial neuropathies causing hoarseness and dysphagia was treated with steroids and immunosuppression, and only one (one of two who also showed imaging abnormalities) was left with residual symptoms, the others recovering in entirety. Patients with cranial neuropathies also had a tendency for mild relapse as the steroid dose was reduced, but this was less evident than in those with optic neuropathy. Methotrexate was used in eight cases and mycophenolate in four. Use of neither drug was associated with adverse effect.

3. Optic neuropathy (27 cases): relapse was common in the early days following initiation of treatment which oftentimes kept the minimum dose of steroids higher than had been hoped. If this recurred more than once, immunosuppression was added. Relapse arose in five cases, and immunosuppression was required in two. Nine returned to normal vision (defined as a normal central acuity and colour vision with a normal 30o automated visual field examination), and eight improved with residual visual impairment. As noted in a previous paper [5], relapse was not a predictor of poor recovery, nor was nadir visual acuity.

*Involvement of the brain by pachymeningitis*

A predominate inflammation of the dura was seen in 23 cases. All received high dose steroids (median 60mg at outset (40 – 100mg)) with immunosuppression. Azathioprine was insufficient in two cases and all ultimately received methotrexate at a median dose of 15mg per week (10 – 20mg). Five received cyclophosphamide at the outset followed by methotrexate, and seven received infliximab when the response to treatment was slow or negligible.

Treatment was well tolerated, with no intercurrent infections, one instance of hepatotoxicity leading to a change to mycophenolate, and the median steroid dose at 2 years was 5 (5 – 10) mg per day. A relapse occurred in one patient after changing cyclophosphamide to methotrexate, and this was treated effectively with infliximab.

Optic neuropathy caused by a compressive lesion at the orbital apex did not respond to treatment; a slight improvement in visual field occurred in two cases whilst the remaining six were unchanged. Those with cavernous sinus masses all improved; in one steroids alone led to complete resolution, in the other two immunosuppression was used and in each case there was a brief steroid responsive relapse as treatment was reduced before the lesion and its symptoms resolved in entirety (figure 1ab). The remaining cases, with lesions arising from the vertex as well as the skull base, recovered well with no residual neurological signs (figure 1cd).

The median MRS following treatment was 0 (0 - 2), median change -2 (0 - -3) (figure 2). One patient relapsed twice on azathioprine and settled well on methotrexate, another as steroids were reduced too quickly, and a third two years after resolution of enhancement when treatment was stopped. The same treatment (methotrexate) allowed the symptoms and the MRI signs to resolve and she has been well since. Figure 3 shows the median time from initiation of treatment to resolution of enhancement on MRI.

*Involvement of the brain by leptomeningitis*

There were 67 cases. All received steroids from diagnosis; the median dose was 60mg (30 – 80mg). Four improved and did not relapse on steroid withdrawal and so received no further treatment. The remainder was treated with immunosuppression. Five received azathioprine; two prescribed by the author on the supposition that the disorder was mild and would not require high dose immunosuppression, and three prior to referral for more aggressive disease; under these circumstances azathioprine was insufficient and was changed. Fifty four received oral methotrexate, at a median dose of 15 (10 – 25) mg per week. Three were changed from methotrexate to mycophenolate when the former caused hepatotoxicity and have remained in remission. Fifteen received infliximab and four cyclophosphamide. Four relapsed as the steroid dose was reduced, prior to immunosuppression starting to take effect. Four were referred some years after the onset of the disease and did not respond to an escalation in treatment with steroids and further immunosuppression. Twelve are at present in the early stages of treatment (less than two years) and each is responding. At two years following initiation of treatment the median steroid dose was 7.5 (5 – 15) mg per day, methotrexate was 15 (10 – 22.5) mg per week and mycophenolate 2000 (1500 – 2500) mg per day.

The median change in MRS following treatment was -2 (0 - -3) and the median MRS was 1 (0 – 5) (figure 2). There was no correlation between change in MRS following treatment and CSF parameters at onset (ρ = 0.05 and 0.019). The median time to resolution of enhancement with each primary treatment is shown in figure 3. It was noted that in most cases atrophy of the affected structures took place as the enhancement resolved (figure 4).

One patient suffered a pneumonia during treatment necessitating hospitalization and treatment withdrawal; her disease returned slowly thereafter but settled when infliximab and mycophenolate were recommenced alongside prophylactic antibiotic therapy. No patient suffered activation of latent tuberculosis. There were two deaths following treatment; one of septicaemia from urinary sepsis and severe lung disease, the other of uncertain cause having become asystolic whilst being monitored in our coronary care unit following a drop attack. Cardiac rhythm had been normal for the preceding 15 hours.

No relapse of systemic or neurological disease has been observed with infliximab therapy. The median duration of treatment was 3 (2 – 5) years with infliximab and 6 (2 – 12) years with methotrexate.

*Involvement of the spinal cord and cauda equina*

Pachymeningeal disorder (4 cases): Each received steroids. Two in whom no response had been made to azathioprine were changed to methotrexate, and the other two were treated with methotrexate from diagnosis. The response to treatment was slow until infliximab was added in each of the four cases; thereafter a rapid resolution of MRI signs was observed. The MRI and symptomatic response to treatment was excellent; the median MRS after two years of treatment was 0 (0 – 1), median change -2 (-1 - -3) (figure 5ab).

Leptomeningeal disorder: Subacute (15 cases): one received no treatment, his condition being inactive. The others all received steroids, 10 methotrexate and two azathioprine. Six also received infliximab when their response to methotrexate was seen to be slow or negligible. The median MRS reduced to 1 (0 – 3), median change -2 (0 - -3), but only two were rendered free of symptoms. Imaging abnormalities were usually not striking and often disappeared following treatment, although with evidence for atrophy (figure 6cd).

Progressive (six cases): each received treatment with steroids and methotrexate; four others also received infliximab. The median MRS reduced to 2.5 (2 – 3), median change -1 (-1 - -2). The progressive deterioration therefore was halted in each case but improvements made were only modest.

Ring enhancing lesions (three cases): One patient responded well to steroids and methotrexate. The other two had a greatly more severe disease and received infliximab. Although substantial gains were made (neither could walk and each now does so with a cane) residual impairments remain. The median MRS was 4 (3 – 5) and the median change -1 (-1 - -2).

Cauda equina sensory syndrome (10 cases): each responded well to steroids, and methotrexate was used to prevent relapse. Two patients had residual symptoms, which improved following the addition of infliximab. Median MRS after treatment was 0 (0 – 1) and median change was -2 (-1 - -2).

Cauda equina motor syndrome (three cases): only one improved; two men with denervated L5 and S1 myotomes remained thus despite treatment. Neither had been treated aggressively at the onset, so it is possible that this syndrome may respond more favourably than it appears herein.

Urinary infections were common in those receiving infliximab who had spinal cord and cauda equina disease, occurring repeatedly in five patients and occasionally (*ie* 1 or 2 in total) in three.

*Isolated Neurosarcoidosis*

These six patients (whose clinical characteristics are described in the companion paper) were treated in the same way as their counterparts with an accompanying systemic disease; the median change in MRS following treatment was -1.5 (0 - -3) in those with isolated neurological disease and -2 (0 - -3) in those with systemic disease, p = 0.5.

**Discussion**

A cohort comprising 166 patients with a rare disease provides important and credible insights into the epidemiology, pathophysiology and natural history of that disorder. In this cohort 165 have been treated with corticosteroids, 139 with immunosuppression of whom 13 received azathioprine, 8 mycophenolate, 122 methotrexate and 9 intravenous cyclophosphamide. Forty one have received treatment with infliximab and two with adalimumab.

There is no doubt that corticosteroids work effectively in sarcoidosis affecting all tissues, including the nervous system [1, 6]. The effectiveness of immunosuppressive agents has been studied in sarcoidosis of the lungs and the eyes [1, 7] and all appear to have a similar efficacy. Methotrexate was the first to be trialed in respiratory disease, and this is why it was used in this cohort; a recent small retrospective study suggests that methotrexate has a marginally greater effectiveness in neurosarcoidosis than mycophenolate [8]. TNFα blockade was first used 15 years ago successfully in treatment resistant systemic sarcoidosis [9], and a year later the first report of its benefit in neurological disease was published [10]. Since then evidence has accumulated which supports the notion that infliximab is effective in all aspects of the disease[7, 11 – 15, 19, 20]. Adalimumab also has an effect but takes longer to work [15]. Golimumab and etanercept have not been shown to be effective in lung and eye disease and etanercept can cause granulomatous disease in patients treated for rheumatic conditions [7, 15, 16].

This series has defined that patients with cranial neuropathies have a mild disease which is unlikely to deteriorate and evolve into a more widespread and infiltrative meningeal disorder and which is associated with a low incidence of MRI and CSF abnormalities. This suggests that the disorder requires only a minor adjustment to the existing treatment of the systemic disease such as a temporary escalation of steroid therapy or the introduction of a mild immunosuppressive agent. In facial neuropathy, imaging abnormalities were seen in only 50% of cases, but these imaging abnormalities whilst implying a more severe form of inflammation were not associated with a poor outcome following treatment. This implies that it is safe to treat thus whilst monitoring carefully for signs of deterioration. Progression to a more severe form of neurological involvement occurred in 31% of those with facial neuropathies and none with more widespread cranial neuropathies. It is possible that this is due to the fact that those with multiple neuropathies were treated more aggressively with immunosuppression as well as steroids than those with mononeuropathies.

Patients with optic neuritis also improve well with treatment and few require more than steroid therapy, but a lower proportion return to normal than those with other cranial neuropathies. The outcome of treatment is discussed in detail in a separate paper [5]. Those with an optic neuropathy associated with dural inflammation do not improve despite a treatment response seen on MRI, suggesting that the underlying disorder is one of compression with ischaemia [5].

Involvement of the brain and spinal cord comes about through two seemingly separate mechanisms; an inflammation of the dura leading to mass lesions and compression of neurological tissue throughout the central nervous system which is associated with seizures and optic neuropathy but with no evidence for spread of inflammation into the brain or cord, and a progressive, infiltrative and destructive leptomeningitis associated with parenchymal inflammation leading to atrophy, hydrocephalus, seizures and residual neurological impairments.

Both forms of neurosarcoidosis respond to treatment with steroids and immunosuppression but it takes years before the MRI visible disorder resolves, and relapse may quickly arise should the treatment be insufficient or be reduced too early on. Relapse is common after short term treatment with TNFα blockade, in both systemic [17, 18] and neurological disease [19, 20]. Relapse tends to occur before the first year following cessation of therapy. The reason for this is likely to be that the condition remains active for much longer than is realised; analysis of serum cytokine concentrations in an early TNFα blockade trial showed that most were not suppressed to within the normal range during treatment and furthermore that concentrations increased again upon cessation of treatment [21].

In this cohort relapse occurred frequently as steroid dose and immunosuppression regime was fine-tuned after diagnosis, but this was a treatment responsive and temporary feature which did not influence outcome. It has not occurred in those treated with infliximab; the reason that this is different to the results of other studies is likely to be that relapse may arise were treatment to be stopped whilst there remains evidence for meningeal enhancement on MRI. Figure 3 shows that this takes years to resolve, and in this unit treatment with immunosuppression and TNFα blockade continues until enhancement resolves and for a further 18 months thereafter, as the frequency of treatment is slowly reduced from 8 weekly to 16 weekly before being stopped. In this cohort patients were treated with infliximab for a mean of three tears.

It is clear from this study and two recently published papers from France [19] and the US [20] suggest strongly that biological agents work well in a severe subtype of the neurological disease. Future research should aim to define whether or not early aggressive treatment can prevent neurological impairment in the leptomeningeal form, the role of early treatment in those with systemic disease in the prevention of neurological complications, in the early aggressive approach to treatment in those who present with multi-system disease in which involvement of the nervous system is already apparent, and of the timing of institution of biological therapies once it becomes manifest, and is likely to improve the natural history and outcome of treatment in this uncommon but important disease.

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Figure 1: Pachymeningitis: T1 weighted axial MRI showing inflammation of the right cavernous sinus causing a fifth and sixth neuropathy (a) before and (b) after treatment with prednisolone and methotrexate over four months, (c) T1 weighted axial MRI showing widespread pachymeningitis before and (d) after treatment with prednisolone, methotrexate and infliximab for nine months.

Figure 2: median MRS before and after treatment\* in pachymeningitis and leptomeningitis of the brain, with interquartile range.

Figure 3: median time for MRI enhancement to resolve *vs* treatment paradigm\* (a) pachymeningitis (b) leptomeningitis of the brain, with interquartile range. The differences are not statistically significant.

[MTX: methotrexate, Cy: cyclophosphamide, Infl: infliximab]

 \*data from those patients who have been treated for greater than two years

Figure 4: Leptomeningitis: T1 weighted coronal MRI showing (a) severe inflammation of the diencephalon and (b) resolution of enhancement and prominent atrophy of the affected area and temporal white matter after two years; T1 weighted axial MRI showing (c) cortical inflammation subjacent to a localised leptomeningitis and (d) atrophy of the affected cortex and white matter after treatment with prednisolone and methotrexate over nine months.

Figure 5: (a, b) T1 weighted sagittal MRI of spinal cord involvement by pachymeningitis showing resolution of enhancement following treatment with prednisolone, methotrexate and infliximab over six months.

Spinal cord atrophy in leptomeningeal spinal cord involvement of the (c) cervical and (d) dorsal spinal cords (T2 and T1 weighted sagittal images respectively) in two other patients previously treated with low dose steroids and mild immunosuppression.