Aggressive Therapy for Neurosarcoidosis

Long-term Follow-up of 48 Treated Patients

Thomas F. Scott, MD; Kristin Yandora, DO; April Valeri, BA; Carol Chieffe, RN, MSCN; Carol Schramke, PhD

Background: Neurosarcoidosis (NS) is a relatively rare neurologic disorder for which no accepted treatment guidelines are available. Treatment with corticosteroids has been described as the primary means of controlling progressive symptoms. However, some physicians have recently advocated early intervention with alternative immunosuppressive therapies in patients who present with disabling symptoms.

Objective: To investigate our experience during the last decade regarding alternative immunosuppressive treatments, including corticosteroids and alternative therapies, in patients with NS.

Design: Observational, retrospective, consecutive case series with longitudinal follow-up.

Setting: Allegheny Neurological Clinic.

Patients: Seventy-eight patients with sarcoidosis were evaluated and classified as having possible, probable, or definite NS according to accepted criteria. Five cases of isolated NS were also included.

Main Outcome Measures: Patients with probable, definite, or isolated NS were scored before treatments and at final follow-up using estimated modified Rankin scores and the Disease Steps in Multiple Sclerosis scales.

Results: Forty-three patients were categorized as having either definite or probable NS according to accepted criteria and an additional 5 as having isolated NS. Thirty patients were categorized as having possible NS and were not included in the analysis of treatment response. Patients had a mean ± SD number of visits of 7.2 ± 6.4 and were followed up for a mean ± SD of 44.1 ± 43.6 months. Twenty patients were treated with pulse and/or maintenance corticosteroids alone. Twenty-six patients were treated with alternative immunosuppressive medications, with 23 of them receiving these medications at the time of diagnosis or within 6 months of the diagnosis of NS. Of the patients treated with alternative immunosuppressive therapies, 18 (69%) improved, 4 (15%) remained stable, and 4 (15%) worsened (including 1 death). Of the patients treated with corticosteroids alone, 7 (35%) improved, 11 (55%) remained stable, and 2 (10%) worsened. Two patients received no treatment.

Conclusions: Approximately half of all patients with NS seen at our clinic were believed to have disabling disease and to be at high risk for disease progression. These high-risk patients were treated with corticosteroids plus alternative immunosuppressive therapy, and favorable outcomes were obtained in almost all patients. Toxic effects related to treatments were minimal.

Few large series of patients with neurosarcoidosis (NS) are available in the literature, and even fewer have examined long-term follow-up of patients or their response to treatment.1-4 No controlled treatment trials have been performed, but corticosteroids are generally accepted as first-line therapy for NS.1,5 Many cases of NS refractory to initial corticosteroid therapy have appeared to respond to alternative immunosuppressive therapy.1,3

Given the reports of treatment failure with corticosteroid therapy in many patients and the toxic effects associated with long-term corticosteroid use, our practice has been to treat selected patients with NS initially with a combination of corticosteroids and alternative immunosuppressive agents, often beginning combination therapy at the time of initial diagnosis. This approach has recently been recommended by a few groups of investigators but only on the basis of experience with a limited number of patients.2,6 Long-term follow-up data from a large group of consecutively treated patients using this approach may provide insight into the treatment and prognosis of NS.

METHODS

We undertook a retrospective review of all patients seen at the Allegheny Neurological Clinic with the diagnosis of sarcoidosis examined between January 1, 1995, and December 31, 2005. All patients presented with neurologic complaints, having been previously diagnosed as hav-
Seventy-eight patients with a diagnosis of sarcoidosis were evaluated in our clinic. Using the criteria of Oksanen,43 patients were classified as having probable or definite NS. Using the more stringent criteria of Zajicek et al, only 35 patients were categorized as having either definite or probable NS. An additional 5 patients had biopsy-proven isolated NS. The results of patient classification by the Oksanen criteria are given in Figure 1. The 30 patients classified as having only possible NS by the criteria of Oksanen were not included in further analysis (analysis for all tables and figures refers to 43 patients who met the criteria of Oksanen and 5 patients with isolated NS). Patient demographics and cerebrospinal fluid (CSF) findings are given in Table 1 and Table 2. Anatomical localizations of biopsy-proven disease are given in Figure 2.

The diagnosis of definite NS according to nervous system histologic analysis was obtained in 12 patients (5 cases of isolated NS, 4 cases in which systemic sarcoidosis was also biopsy proven, and 3 cases in which systemic sarcoidosis was demonstrated by chest imaging and elevated angiotensin-converting enzyme levels; Figure 1). Existing criteria do not encompass cases that involve NS limited to the central nervous system, but we included 5 such cases. These patients underwent biopsy primarily to rule out neoplastic processes but otherwise did not present differently from the patients with NS and systemic sarcoidosis. The diagnosis of probable NS by the criteria of Zajicek et al (n=28) was obtained by a combination of typical clinical features with typical MRI findings, inflammatory CSF changes, or both. All patients with NS deemed severe enough to warrant treatment with immunosuppression had either isolated NS or met the criteria of Zajicek et al. The MRI findings for patients with isolated, definite, or probable NS are given in Figure 3. The CSF findings were typical, as described in many previous studies. The CSF angiotensin-converting enzyme levels were obtained in 12 patients and were elevated in 2. Elevation of CSF angiotensin-converting enzyme levels was not deemed useful in providing the diagnosis in any case. Chest imaging was often useful in suggesting the diagnosis of NS, with a positive result on chest x-ray examination seen in 17, on chest computed tomogram in 9, and on gallium scan in 3. In 4 cases, chest imaging provided evidence of systemic sarcoidosis after NS was detected by central nervous system biopsy. A postmortem diagnosis of probable NS occurred in a patient with chronic meningitis in whom splenic involvement was found at autopsy.

Patients with probable, definite, or isolated NS had a mean±SD number of visits of 7.2±6.4 (range, 2-27) and were followed up for a mean±SD of 44.1±43.6 months (range, 4-141 months). Two patients received no treatment (both with probable NS). Nineteen patients were treated with maintenance corticosteroids alone, with only 2 of these patients receiving high-dose intravenous corticosteroids at onset. Twenty-six patients were considered to be at high risk for progression because they presented with severe central nervous system involvement in NS (intracranial lesions, hydrocephalus, myelopathy, seizures, or encephalopathy) were treated with alternative immunosuppressive medications in addition to corticosteroids. Alternative immunosuppressive medications consisted of cyclophosphamide, azathioprine, and methotrexate.

RESULTS

Seventy-eight patients with a diagnosis of sarcoidosis were evaluated in our clinic. Using the criteria of Oksanen, 43 patients were classified as having probable or definite NS. Using the more stringent criteria of Zajicek et al, only 35 patients were categorized as having either definite or probable NS. An additional 5 patients had biopsy-proven isolated NS. The results of patient classification by the Oksanen criteria are given in Figure 1. The 30 patients classified as having only possible NS by the criteria of Oksanen were not included in further analysis (analysis for all tables and figures refers to 43 patients who met the criteria of Oksanen and 5 patients with isolated NS). Patient demographics and cerebrospinal fluid (CSF) findings are given in Table 1 and Table 2. Anatomical localizations of biopsy-proven disease are given in Figure 2.

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and 2 (10%) worsened (Figure 5). The median STEPS score of all patients both before and after treatment was 1 (range, 1-6). The median modified Rankin score was 2 before treatment (range, 0-4) and 1 after treatment (range, 0-5). Although cognitive complaints were not quantified, several patients reported improved cognition after treatment.

Further analysis of pretreatment Rankin and STEPS scores showed higher median scores in the group of patients selected for alternative immunosuppressive treatments compared with patients treated with corticosteroids alone (median Rankin score, 2 vs 1; mean STEPS score, 2 vs 1). The differences between these groups according to both Rankin and STEPS scores were significant (P=.002 and .006, respectively, using the Mann-Whitney U test). Differences between pretreatment and posttreatment disability scores were examined in patients treated with corticosteroids alone and in patients treated with alternate immunosuppressive medications. A significant decline in disability scores was seen in pa-

tients treated with alternative immunosuppressive medications (final median Rankin score, 1; final mean STEPS score, 1) using the Wilcoxon signed rank test (P=.008 and .045, respectively), but no decline in scores was seen in patients treated with corticosteroids alone.

Corticosteroids were initiated at 60 to 80 mg/d, occasionally following a high-dose pulse given throughout a few days. In most patients, corticosteroid doses were tapered to 20 to 30 mg/d by month 4. Of those treated with corticosteroids only, 8 of 19 patients were weaned off corticosteroids completely by 2 to 3 years (2 were lost to follow-up). Dose ranges of methotrexate (n=18 patients) were 7.5 to 15 mg/wk, with 8 patients weaned off methotrexate throughout 12 to 36 months (while simultaneously being weaned off corticosteroids). One patient was taking methotrexate only briefly and was changed to azathioprine because of severe nausea.

Table 1. Demographics of the 48 Study Patients

<table>
<thead>
<tr>
<th>Treatment Criteria</th>
<th>Alternative Immunosuppression</th>
<th>Corticosteroid Only</th>
<th>No Treatment</th>
<th>All Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female/male</td>
<td>15/6</td>
<td>15/11</td>
<td>1/1</td>
<td>31/17</td>
</tr>
<tr>
<td>Mean disease duration, mo</td>
<td>65.1</td>
<td>91.2</td>
<td>168.0</td>
<td>83.5</td>
</tr>
<tr>
<td>Mean follow-up, mo</td>
<td>32.9</td>
<td>54.0</td>
<td>24.0</td>
<td>44.1</td>
</tr>
<tr>
<td>Mean No. of office visits</td>
<td>4.7</td>
<td>9.7</td>
<td>3.5</td>
<td>7.2</td>
</tr>
</tbody>
</table>

Table 2. CSF Results*

<table>
<thead>
<tr>
<th>Treatment Criteria</th>
<th>Alternative Immunosuppression</th>
<th>Corticosteroid Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF protein level</td>
<td>6/11 (54)</td>
<td>17/21 (81)</td>
</tr>
<tr>
<td>CSF WBC count</td>
<td>6/12 (50)</td>
<td>11/19 (58)</td>
</tr>
<tr>
<td>CSF ACE level</td>
<td>0/0</td>
<td>2/8 (25)</td>
</tr>
<tr>
<td>CSF oligoclonal bands</td>
<td>3/8 (38)</td>
<td>1/4 (25)</td>
</tr>
<tr>
<td>CSF IgG level</td>
<td>3/7 (43)</td>
<td>5/6 (82)</td>
</tr>
</tbody>
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*Data are presented as number/total number (percentage).

Abbreviations: ACE, angiotensin-converting enzyme; CSF, cerebrospinal fluid; WBC, white blood cell.

Figure 2. Anatomical localization of biopsy-proven sarcoidosis.

Figure 3. Magnetic resonance imaging findings in patients with probable or definite neurosarcoidosis.

Figure 4. Frequency of symptoms of neurosarcoidosis in 48 patients.

Table 2. CSF Results*
nosuppressants, and a ventriculoperitoneal shunt. This patient treated for several years with corticosteroids, immunosuppressive therapy), and 2 other patients have required adjustments in immunosuppressants or corticosteroids before being weaned off these medications as tolerated throughout a total of 12 to 36 months. Nine of 26 patients treated with alternative immunosuppressive medications within 6 months of presentation to our clinic (treatment with alternative immunosuppressive agents in 6 patients before longer-term oral immunosuppressants. One of these cyclophosphamide-treated patients was unable to tolerate either methotrexate or azathioprine because of nausea and was treated with additional cyclophosphamide pulses and corticosteroids. For patients who continue therapy, we plan to continue weaning patients off these medications as tolerated throughout a total of 12 to 36 months. Nine of 26 patients treated with alternative immunosuppressive therapy have been weaned from all therapy, including corticosteroids. Thus far, only 1 patient has required reinstitution of therapy for relapse (after 1 year without therapy), and 2 other patients have required adjustments of immunosuppressants or corticosteroids because of worsening symptoms. Another patient treated with immunosuppressants has remained neurologically stable for 1 year but has had slightly worsening cutaneous and pulmonary sarcoidosis.

The 2 deaths seen in our patient group involved syndromes of chronic meningitis. The first case involved an elderly patient treated for several years with corticosteroids, immunosuppressants, and a ventriculoperitoneal shunt. This patient failed attempts to be weaned off medications and eventually succumbed to uncontrolled urosepsis. The second patient was followed up in our clinic only briefly and received no corticosteroids or other therapy for NS because the diagnosis was made postmortem. This patient died of central cerebral herniation immediately after a lumbar puncture, which revealed extremely high intrathecal pressure. Autopsy revealed granulomatous lesions in the spleen. Surprisingly, the meninges and brain appeared normal (no inflammation), despite the finding of CSF pleocytosis and a high CSF protein concentration.

Magnetic resonance imaging was performed on a variety of scanners with field strengths ranging from 0.5 to 1.5 T, with nearly all patients receiving postcontrast imaging with gadolinium. A systematic review of evolutionary MRI changes is ongoing. Many patients exhibited improved MR status during treatment, including decreased size of white matter lesions on T2-weighted imaging, and resolution of most enhancing lesions of the parenchyma, dura, and pia-arachnoid. A representative case is shown in Figure 6.

Monitoring of treatment toxic effects was standard for patients treated with long-term alternative immunosuppressive therapies, including monthly liver function tests, complete blood cell counts and differential performed on cyclophosphamide-treated and azathioprine-treated patients, and bimonthly testing of methotrexate-treated patients. Mild leukopenia (total white blood cell count of 3000-4000/µL) was seen in 6 patients, and doses were adjusted because of moderate leukopenia (total white blood cell count of 2000-2900/µL) in 2 patients. Mild to moderate elevations in liver function test results (transaminase levels up to 3 times normal) were seen in 11 patients. Steroid toxic effects were typical and did not require hospitalization in any patient.

DELAY OF DIAGNOSIS

Most patients had mild neurologic symptoms likely related to undiagnosed NS for months or years before presenting to our clinic with more prominent symptoms of NS. The mean±SD time from onset of neurologic symptoms until diagnosis in our clinic was 37±11 months. A previous diagnosis of NS was seen in only 5 patients at the time of presentation to our clinic. A rapid onset of severe neurologic symptoms leading to a diagnosis of NS within 1 month of symptom onset was seen in only 6 patients.

TIMING OF ALTERNATIVE IMMUNOSUPPRESSIVE TREATMENTS

Our tendency to initiate early aggressive treatment of patients with disabling NS was reflected in the records of the 26 patients treated with these therapies as follows: (1) the average time from evaluation in our clinic until treatment with alternative immunosuppressive agents in addition to corticosteroids was 10 weeks; (2) more than half of these patients (14 of 26) were given the initial diagnosis of NS in our clinic and began alternative immunosuppressive therapies with corticosteroids immediately; and (3) all but 3 of these 26 patients were treated with alternative immunosuppressive medications within 6 months of presentation to our clinic (treatment with...
long-term corticosteroids alone was initially attempted in only 3 patients, who eventually were thought to need more aggressive therapy). Patients with histologically verified NS who underwent intracranial or intraspinal biopsy (n=11) were all deemed sufficiently impaired to warrant intervention with alternative immunosuppressive treatment (as initial treatment in 9 patients and in 2 patients treated initially with surgery alone whose conditions deteriorated and were subsequently treated with alternative immunosuppressive agents).

**COMMENT**

Long-term follow-up studies of patients with NS suggest that patients with disease limited to cranial neuropathy or peripheral neuropathy syndromes are at low risk for progression, with a notable exception being occasional cases of progressive optic neuropathy. Patients with aseptic meningitis, a relatively common clinical manifestation of NS, may also be at low risk for long-term disability. However, development of hydrocephalus due to chronic meningitis may be an ominous sign. Patients with symptomatic intracranial disease also represent a group of patients at increased risk for progression. One report suggests that patients with seizures and intracranial disease are at increased risk. We noted that none of our patients designated as having possible NS were referred back to our clinic for further evaluation, indicating that these patients may be unlikely to progress to probable or definite NS. Some of the patients with possible NS underwent imaging procedures that revealed mild nonspecific white matter changes, which could be related to the NS.

Our case series contained relatively few cases of peripheral nervous system sarcoidosis, perhaps because of a referral pattern of these patients, who tended to be mildly affected and not referred to specialty clinics. In fact, all patients evaluated in our clinic had central nervous system and/or cranial nerve involvement; peripheral nerve involvement was the major manifestation of NS in only 1 patient. Many patients with central nervous system disease and cranial neuropathies were mildly affected and had minimal or no evidence of disease progression during the follow-up period. Because only patients who met the criteria of Zajicek and colleagues were considered to have sufficiently severe symptoms to warrant intervention with alternative immunosuppressive therapies, we considered omitting patients who did not meet these criteria. However, we decided that inclusion of probable cases of NS that met other criteria would provide a more complete picture of the spectrum of NS seen in our clinic.

We restricted the use of alternative immunosuppressive therapies to patients with a demonstrable degree of disability (exhibiting neurologic deficits that interfered with gait or other motor functions or cognition or significantly impaired activities of daily living due to other problems such as seizures) related to central nervous system involvement in NS. A few of these patients were referred to us after their conditions deteriorated while taking corticosteroids alone, but most were newly diagnosed as having NS. Ideally, a controlled study would assess the efficacy of our strategy vs other treatment regimens. Such

![Figure 6. T1-weighted enhanced magnetic resonance image of a patient with ataxia, seizures, and cognitive dysfunction before (A) and 7 months after treatment (B) showing resolution of multiple enhancing lesions. The patient's clinical picture also improved, with complete normalization of her neurological examination results.](https://www.archneurol.com/content/64/5/695.full.pdf)
a study would likely require multiple centers. Studies that assess outcomes in NS at present are few and uncontrolled, and they are insufficient for assessing the clinical efficacy of our approach. However, the relatively large group of patients we studied appears to have done well, with only 4 (15%) of 26 patients treated with immunosuppression therapy progressing to an increased level of disability after treatment (including 1 death). Most but not all of our patients with definite NS presented with symptoms sufficiently severe to warrant treatment beyond corticosteroids. By comparison, many patients with probable NS also presented with symptom severity that warranted early aggressive therapy. Therefore, the distinction between definite and probable NS was not critical in determining treatment in this series.

Our study group included 2 patients who died, calling attention to the potential complications of sarcoid meningitis. Given that 1 patient deteriorated suddenly and died unexpectedly because of cerebral herniation in the setting of headache and very high intracranial pressure secondary to chronic sarcoid meningitis, we routinely instruct our patients with NS to report headaches for possible urgent evaluation. As reported previously by others, sarcoid meningitis that results in hydrocephalus may represent a particularly malignant scenario. However, 3 of our patients were successfully treated with a ventriculoperitoneal shunt, corticosteroids, and methotrexate. The use of all medications was eventually stopped in 2 patients, who are now stable and medication free and have demonstrated only moderate impairment of gait during the past 2 years.

The concept of isolated NS has been reviewed in other reports, although current criteria do not encompass this aspect of the spectrum of sarcoidosis. The frequency of isolated NS seen in our series in 5 (10%) of 48 patients is close to that reported in another recent large series.

Other investigators have noted the preponderance of both symptomatic and asymptomatic white matter lesions in NS and the close resemblance of these lesions to multiple sclerosis plaques in some cases. These lesions are often rounded or ovoid but may also have a more nonspecific appearance. In our series, deep white matter lesions were the most frequent neuroradiologic finding on MRI, in agreement with previous reports.

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CONCLUSIONS

The study of treatments in NS has been limited to descriptions of responses to open-label corticosteroids and alternative immunosuppressive agents in individual cases and some small patient groups. Most physicians recommend corticosteroid therapy as initial treatment for all unstable patients with NS, reserving alternative immunosuppressive treatment such as azathioprine or methotrexate for patients who do not respond. However, a few investigators have recommended that more aggressive treatments be considered as initial therapy for patients with central nervous system disease who appear to be at high risk for corticosteroid failure or corticosteroid adverse effects. Considering the potential toxicity of the long-term corticosteroid regimens that are generally used in patients with NS, we believe that the risk of increased toxicity from so-called steroid-sparing alternative immunosuppressive agents is minimal. Significant benefits are suggested by our experience and that of others in terms of treatment response to alternative immunosuppressive agents. Patients with mildly symptomatic NS were treated with corticosteroids alone and also did well but were expected to do so given our understanding of the prognosis in NS. For the past decade, our treatment strategy in NS has been to select patients at high risk for permanent disability and to consider initial treatment with a combination of corticosteroids and an alternative immunosuppressive agent. These treatments have been well tolerated and associated with good outcomes in most of our patients.

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Correspondence: Thomas F. Scott, MD, 420 E North Ave, Suite 206, Pittsburgh, PA 15212 (tscott@wpahs.org).

Author Contributions: Study concept and design: Scott, Yandora, and Valeri. Acquisition of data: Scott, Yandora, Valeri, and Chieffe. Analysis and interpretation of data: Scott, Yandora, and Schramke. Drafting of the manuscript: Scott, Yandora, and Schramke. Critical revision of the manuscript for important intellectual content: Scott, Yandora, Valeri, Chieffe, and Schramke. Statistical analysis: Scott, Yandora, Valeri, and Schramke. Administrative, technical, and material support: Scott, Yandora, Valeri, and Chieffe. Study supervision: Scott and Yandora.

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