We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



14

Neurological Sarcoidosis

J. Chad Hoyle and Herbert B. Newton
Departments of Neurology and Neurosurgery,
The Ohio State University Medical Center and James Cancer Hospital,
USA

1. Introduction

Sarcoidosis is a granulomatous, inflammatory disease that can affect multiple systems of the body. Most commonly this involves the lungs, skin, and eyes, but also can affect the nervous system in about 5% of cases (Delaney1977, Stern et al 1985). Neurological sarcoidosis may be associated with virtually any aspect of the nervous system, but just like the predilection for certain organ systems in systemic disease, neurological involvement also may demonstrate characteristic clinical patterns to aid in the recognition of the disorder. This is especially important because the presenting manifestations may be neurological in nearly 50% of these patients (Stern et al 1985). The first large review of the trends of clinical involvement of the nervous system in sarcoidosis was outlined over 60 years ago (Colover 1948). Subsequent reviews and case reports have built on that foundation. This chapter will outline the clinical manifestations, diagnostic considerations, and management options, including new trends in therapy of neurological sarcoidosis.

2. Clinical manifestations

The most classic clinical patterns of nervous system involvement in sarcoidosis include cranial neuropathy, meningeal based disease, and hypothalamic-pituitary axis symptomatology. Cranial neuropathy is the most common neurological deficit with an incidence of 50 to 75% of patients (Delaney 1977, Stern et al 1985). In general, meningeal based disease is a common hallmark of neurosarcoidosis and can manifest in a variety of ways as outlined below. Hypothalamic-pituitary axis involvement may yield only relatively nonspecific symptomatology, but can be a frequent and important manifestation, as well.

The most common cranial neuropathy is a facial palsy. In hindsight, the first historically described cases occurred early in the 20th century, when unusual presentations of parotid enlargement, uveitis, and facial palsies were described (Heerfordt 1909). Years later facial palsy was documented in half of neurosarcoidosis patients (Colover 1948, Stern et al 1985), making it the most predominant clinical association. A third of these cases are bilateral (Colover 1948, Stern et al 1985), and those presentations or recurrent facial palsy in general should trigger a suspicion for a secondary cause of facial palsy, such as Lyme disease or neurosarcoidosis.

The second most common cranial neuropathy is of the optic nerve. The incidence of this presenting complaint is rather high, and actually in more recent papers, some have

described this as being even more common than facial palsy (Pawate et al 2009, Joseph and Scolding 2009). Referral bias was considered as a cause of this as Pawate's data came from a multiple sclerosis center, whereas Stern's prior data noted above came from a sarcoidosis clinic. Regardless, sarcoidosis needs to be in the differential of secondary causes of optic neuritis within the appropriate clinical context, and bilateral optic neuritis, in particular, may herald an even stronger neurological suspicion for sarcoidosis, along with other conditions that may classically present that way, such as neuromyelitis optica. Unfortunately, bilateral optic neuritis tends to have a markedly worse prognosis for recovery compared to unilateral optic neuritis (Pawate et al 2009). Of note, it is important to keep in mind that the most common ocular symptoms in sarcoidosis are still primary ophthalmological manifestations, such as uveitis.

The eighth cranial nerve is affected in up to one fifth of patients. This involvement tends to be bilateral, and appears to be related to granulomatous meningitis in most cases. Patients may experience hearing loss or have vestibular dysfunction. This may present suddenly or with a fluctuating course. Recovery of function is less common than with facial palsies. (Stern et al 1985) The most common extraocular muscle palsy is of the sixth nerve (Joseph and Scolding 2009). Trigeminal neuropathies have also been well described in association with sarcoidosis (Armin A and Balderacchi JL 2010). Cranial nerve nine and ten palsies may result in dysphagia, hoarseness, or vocal cord paralysis (Delaney 1977). Though an ENT study documented neurosarcoidosis of the vagus nerve to be rare in their general patient population, they noted it should still be considered in the differential diagnosis of vocal cord paresis or paralysis (Alon and Ekbom 2010). Although felt to be uncommon, decreased smell might be an underreported complication given that the 1st cranial nerve is not commonly tested on examination. Significant, symptomatic anosmia from sarcoidosis is more commonly encountered in patients with significant generalized disease and it can be refractory to treatment (Aubart et al 2006). Essentially, any cranial nerve may be affected by the granulomatous infiltration of sarcoidosis, though the rest of the cranial nerves not outlined above would only very rarely be involved.

Meningeal based disease is another classic finding of neurosarcoidosis. In fact this meningeal based disease is also not only responsible for many of the cranial neuropathic complications, but presents in a variety of other ways, as well. Significant basilar disease can be associated with a polycranial neuropathy from meningeal infiltration. Meningeal disease may cause headache related to acute aseptic or chronic meningitis. In one large review series at the Mayo Clinic, chronic meningitis was actually the most common initial manifestation of neurosarcoidosis (Aksamit and Norona 1999). If cerebrospinal fluid flow becomes obstructed, then headache might also be a manifestation of hydrocephalus. Weakness, pain, and sensory dysfunction can be seen in some cases with polyradicular involvement from spinal meningeal infiltration. All together, some form of meningeal involvement is a very common and suggestive feature of neurological sarcoidosis.

Hypothalamic-pituitary axis symptomatology can be rather nonspecific, but taken into context with other features of neurosarcoidosis, it might help tip the balance of clinical evidence to proceed further with testing for sarcoidosis. Diabetes insipidus is considered the most common manifestation, accounting for half of all neuroendocrine abnormalities (Chapelon et al 1990). Of note, an organic primary polydipsia may also be the cause of polyuria and polydipsia, and hypercalcemia from sarcoidosis can cause nephrogenic diabetes insipidus (Stuart et al 1980). Other relatively common neuroendocrine

manifestations of sarcoidosis include amenorrhea or galactorrhea. Serum prolactin levels have been high in up to a third of patients in general with sarcoidosis (Turkington and Macindoe JH 1972), and that unexpected high percentage could reflect that some degree of subclinical neurological involvement is associated with many more systemic sarcoidosis patients than previously thought. A more complete list of possible endocrine manifestations of sarcoidosis includes morbid obesity, dysregulation of body temperature, insomnia, personality change, SIADH, diabetes insipidus, hyperprolactinemia, hypothyroidism, hypoadrenalism, growth hormone deficiency, and impaired counter-regulatory response to hypoglycemia (Porter et al 2003).

In addition to the above classical neurological manifestations of sarcoidosis, there are several other neurological entities that are seen with intermediate frequency and less specificity. This may include seizures, which have been reported in 10% to 17% of patients (Delaney 1977, Pawate et al 2009, Joseph and Scolding 2009). Seizures correlate with a worse prognosis overall, likely as a reflection of more significant underlying parenchymal disease. In addition to seizures, central nervous system granulomatous mass lesions can cause headache, lethargy, or other localization related symptomatology. (Stern et al 1985) Spinal cord disease also can present with intermediate frequency. Leptomeningeal infiltration in the region of the spinal cord is associated with sarcoidosis, but intraparenchymal infiltration can occur, too, causing fusiform spinal cord enlargement, focal or diffuse intramedullary disease, or spinal cord atrophy (Junger et al 1993). Based on recent reports, greater than 15% of initial clinical presentations of neurosarcoidosis can be related to myelopathy or spinal cord disease in general (Pawate et al 2009, Joseph and Scolding 2009). A longitudinal myelitis can be the presenting symptom of neurosarcoidosis, making this a consideration with other longitudinally extensive cord inflammatory syndromes (Sierra-Hidalgo et al 2010), such as neuromyelitis optica or connective tissue disorders such as Sjogren's disease or Lupus. Neuropsychiatric disorders also have an intermediate incidence. The symptomatology related to this can include encephalopathy, psychosis, depression, bipolar disorder, apathy, irritability, and lethargy (Joseph and Scolding 2007, De Mulder and Vandenberghe 2008, Spiegel et al 2010, Friedman and Gould 2002, Bona et al 1998, O'Brien et al 1994, Sabaawi et al 1992). One should consider these neuropsychiatric symptoms to potentially be organic and possibly responsive to immunomodulatory therapy rather than just primary psychological causes. Interestingly, a patient has been described as having abnormal cerebrospinal fluid with isolated psychiatric symptoms (Gilmore et al 1980). Peripheral nervous system involvement occurs in about 15% of neurosarcoidosis cases and typically has a better prognosis than central nervous system involvement (Delaney 1977). A subacute generalized axonal sensorimotor polyneuropathy is the typical subtype of polyneuropathy seen in sarcoidosis (Zuniga et al 1991), but one must take into account that asymmetrical peripheral neuropathic limb symptomatology can be seen with polyradiculoneuropathy, which is a very well documented presentation in this disorder (Burns et al 2006). Sarcoidosis can also cause mononeuropathy with a notable increased incidence of carpal tunnel syndrome (Niemer et al 2001) among other mononeuropathy presentations. A more diffuse mononeuritis multiplex picture may occur (Zuniga et al 1999, Garg et al 2005), purely sensory neuropathy may be seen, and even rare associations of lumbosacral plexopathy have been encountered (Zuniga et al 1991). Small fiber neuropathy needs to be considered in sarcoidosis, as well (Tavee and Culver 2011, Hoitsma et al 2002). Finally, there have even been reports of Guillain-Barre like illnesses associated with neurosarcoidosis (Fahoum et al 2009).

Muscle involvement symptomatically ranges from less than 1% to potentially up to 26% of patients (Oksanen 1986, Chapelon et al 1990). Symmetrical myopathic weakness or myalgias can be experienced. There may be isolated palpable nodules within the muscle. More often, though, muscle involvement is asymptomatic. This asymptomatic involvement can be seen in up to 50% of muscle biopsies (Delaney 1977). Vascular infiltration is remarkably rare, with a very low incidence of hemorrhage or stroke. Movement disorders other than cerebellar ataxia are very rare, with only isolated reports of extrapyramidal symptoms from basal ganglia involvement, such as chorea, hemiballism, and Parkinsonism (Delaney 1977).

To summarize, the classical clinical findings include cranial neuropathy, meningeal based disease, and hypothalamic-pituitary axis symptomatology. Intermediate frequency symptomatology, such as seizures, spinal cord disease, peripheral neuropathy, muscle disease, or neuropsychiatric manifestations can be rather non-specific. Early recognition of systemic signs and symptoms of ocular disease, lung disease, and skin disease increases the yield of recognizing the disorder. In addition, 30% of patients present with more than one neurological manifestation (Stern et al 1985), which may increase the clinical context for suspecting the diagnosis, even in cases without systemic disease. As there is no gold standard test, except for biopsy, clinical acumen is necessary to combine clinical suspicion with optimal understanding of non-invasive test strategies to select appropriate patients without a known diagnosis of sarcoidosis for pathological tissue studies to confirm the diagnosis. The next section will expand upon diagnostic considerations.

Classical features
Cranial neuropathy
Meningeal based disease
Hypothalamic-pituitary axis dysfunction
Intermediate frequency features
Seizures
Encephalopathy/psychiatric symptomatology
Spinal cord disease
Peripheral neuropathy

Table 1. Major clinical features of neurosarcoidosis

Most common cranial neuropathies in sarcoidosis in order of frequency
Bell's palsy (Cranial Nerve 7)
Optic neuropathy/neuritis (Cranial Nerve 2)
Vestibulocochlear neuropathy (Cranial Nerve 8)
Other cranial nerves with intermediate frequency
Cranial Nerves 5, 6, 9, or 10

Table 2. Cranial nerve involvement in sarcoidosis

3. Diagnostic considerations

Once neurosarcoidosis is considered in the differential diagnosis, the next step is to further evaluate this with non-invasive supportive diagnostic testing. MRI with contrast, lumbar puncture, and ACE levels should all be considered in the initial work-up, though these tests lack specificity. In cases without systemic involvement, routine chest imaging should be undertaken at a minimum, and further supportive testing such as gallium scanning or bronchoalveolar lavage should also be considered. Nevertheless, pathological confirmation of tissue, demonstrating non-caseating granulomas, is necessary to justify treatment for this disorder. The proposed criteria for the diagnosis of neurosarcoidosis has been partitioned into definite, probable, or possible disease (Zajicek et al 1999). Definite disease consists of a clinical presentation compatible with neurosarcoidosis, exclusion of other possible causes, and confirmation with biopsy of nervous system tissue, such as the meninges or another source. Probable disease is defined as a clinical presentation compatible with neurosarcoidosis, non-invasive neurodiagnostic support of the diagnosis, exclusion of other possible causes, and evidence of systemic sarcoidosis by biopsy. Possible neurosarcoidosis is defined as a clinical presentation compatible with neurosarcoidosis clinically and with noninvasive neurodiagnostic studies, along with exclusion of other possible causes.

Developing a focused differential diagnosis based on the site of neurological involvement is critical to effectively excluding other disorders that may mimic neurosarcoidosis. Classical disease that involves a meningeal process would require the exclusion of infectious and malignant etiologies. Examples of this would range from chronic infectious processes, such as fungal infections and tuberculosis to malignant processes such as carcinomatous or lymphomatous meningitis. These would all be highly pertinent considerations in patients with basilar infiltration causing polycranial neuropathies. Restricted cranial nerve lesions, such as unilateral Bell's palsy may be clinically indistinguishable from idiopathic cases, though recurrent or bilateral disease should invoke consideration of secondary causes such as sarcoidosis, Lyme disease, or a rare disorder, Melkersson-Rosenthal syndrome. Similarly, unilateral optic neuritis might suggest multiple sclerosis in the differential, whereas bilateral disease increases the suspicion of sarcoidosis or other disorders, such as neuromyelitis optica. Transverse myelitis might be difficult to distinguish from idiopathic demyelination or multiple sclerosis, but longitudinally extensive lesions, which can be seen in neurosarcoidosis, bring several diagnostic considerations to the forefront, such as neuromyelitis optica, connective tissue disorders such as Sjogren's or Lupus, or vascular disorders, such as dural A-V fistula. White matter disease on MRI would necessitate differentiation from multiple sclerosis, nonspecific vascular disease, inflammatory/vasculitic etiologies, or infectious considerations like Lyme disease. HIV can masquerade as having many of the features of neurosarcoidosis, in general. Multi-systemic disease may suggest other uncommon syndromes, such as amyloidosis. Mass lesions in the brain from sarcoid granulomas need differentiation from other lesions such as tumor or abscess. Dural lesions can mimic meningioma. A vasculopathy appearance with encephalopathy must be differentiated from CNS vasculitis or neurosyphilis. Finally, peripheral nervous system involvement is much more nonspecific. With peripheral neuropathic processes, the differential diagnosis depends on the location, neurophysiology, and timing of the neuropathy. For instance, the most common polyneuropathy of an axonal sensorimotor

polyneuropathy might be difficult to distinguish from the common causes of metabolic polyneuropathy, such as diabetes, thyroid disease, vitamin deficiency, connective tissue disease, toxins, or monoclonal gammopathies associated with or without significant underlying hematological disease. A subacute onset might help lean more towards an acquired, inflammatory cause in the differential, though. With a mononeuritis multiplex picture, one would need to differentiate between vasculitis, diabetes, or less common infectious etiologies such as hepatitis, Lyme, or HIV. Isolated mononeuropathy would be difficult to distinguish from common entrapment neuropathies. As mentioned above, an acute polyneuropathy with a Guillain-Barre phenotype can be seen. A Guillain-Barre like illness with unexpected cerebrospinal fluid pleocytosis (Fahoum et al 2009) in addition to the expected high protein level might signal other considerations like HIV or sarcoidosis as underlying etiologies.

Compatible epidemiological features such as younger patients and an African American predominance can be clues, though very non-specific given the differential diagnosis above. In cases of known systemic sarcoidosis, the diagnosis mainly entails ruling out other etiologies of neurological involvement, especially infectious causes given these patients may already be immunosuppressed. In cases without systemic involvement, the diagnosis can be challenging and further experience with the details of the diagnostic workup is necessary. We will discuss the noninvasive diagnostic strategies first. This will include MRI studies with contrast, cerebral spinal fluid studies, ACE levels, chest imaging, and gallium studies. Analyzing five large case reviews (Zajicek et al 1999, Christoforidis et al 1999, Aksamit and Norona 1999, Pawate et al 2009, Joseph and Scolding 2009), the following trends and details regarding specific diagnostic tests emerge.

MRI of the brain with contrast, as well as the spinal cord, if symptomatology and exam findings suggest localization there, is a key to the diagnostic workup. The sensitivity rate for an abnormal brain MRI with contrast in patients with symptoms referable to the central nervous system may be as high as 80 to 90% (Christoforidis et al 1999, Pawate et al 2009). Overall, spinal cord abnormalities are seen in 10-20% of cases (Zajicek et al 1999, Pawate et al 2009). However, when spinal cord symptomatology is present, imaging is abnormal in roughly 60-70% of cases (Aksamit and Norona 1999, Pawate et al 2009).

On MRI of the brain, nonspecific white matter lesions are common, with roughly 40% of cases showing these findings (Zajicek et al 1999). Patients with isolated white matter disease tend to have a good prognosis. Nevertheless, this is a very nonspecific finding and a contrast enhanced study with gadolinium will demonstrate much more of the classical features of sarcoidosis. Meningeal enhancement is quite common and can be seen in nearly 40% of cases (Zajicek et al 1999). There are multiple other enhancing abnormalities that can be encountered, too. Strictly dural enhancement may be seen, as well as isolated cranial nerve enhancement, focal parenchymal enhancement associated with a white matter lesion or with a focal mass (in general parenchymal enhancement has a relative predilection for the hypothalamic-pituitary axis), or periventricular radial vascular enhancement. In 10-15% of neurosarcoidosis patients, hydrocephalus can be present (Zajicek et al 1999). Vasculitic infarcts are very rare, but do occur (Pawate et al 2009). Interestingly, 40% of cranial nerve deficits were not associated with their respective cranial nerves having enhancement on MRI, though conversely 44% of patients had MRI evidence of cranial nerve involvement with no symptoms related to that radiologically affected site (Christoforidis et al 1999). The

findings of Christoforidis also noted that even though hypothalamic-pituitary axis enhancement is not a rare finding on imaging, 50% of patients with symptoms related to the hypothalamic-pituitary axis had no abnormal findings on imaging in that region. Spinal cord lesions most typically consist of meningeal enhancement, spinal cord swelling, or enhancing myelitis of the cord (Pawate 2009).

Common MRI Brain features of neurosarcoidosis
Non specific white matter changes
Meningeal thickening/enhancement
Cranial nerve enhancement
Parenchymal enhancement of white matter lesion or a focal mass
Parenchymal enhancement has a relatively greater predilection for the hypothalamic-pituitary axis
Hydrocephalus
MRI Spine features of neurosarcoidosis
Meningeal or radicular enhancement/thickening
Cord swelling
Myelitis (often enhancing)

Table 3. Imaging findings in neurological sarcoidosis

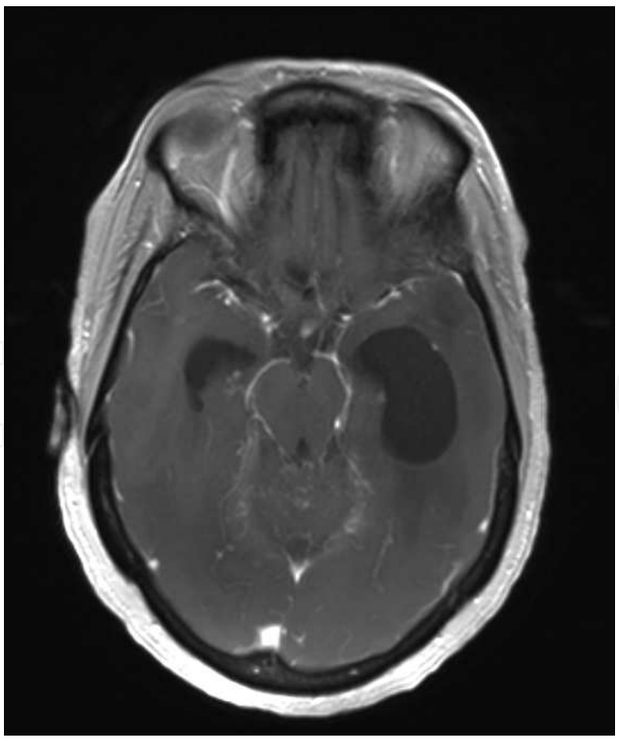


Fig. 1. Gadolinium enhanced MRI of the brain demonstrating basilar leptomeningeal enhancement and hydrocephalus

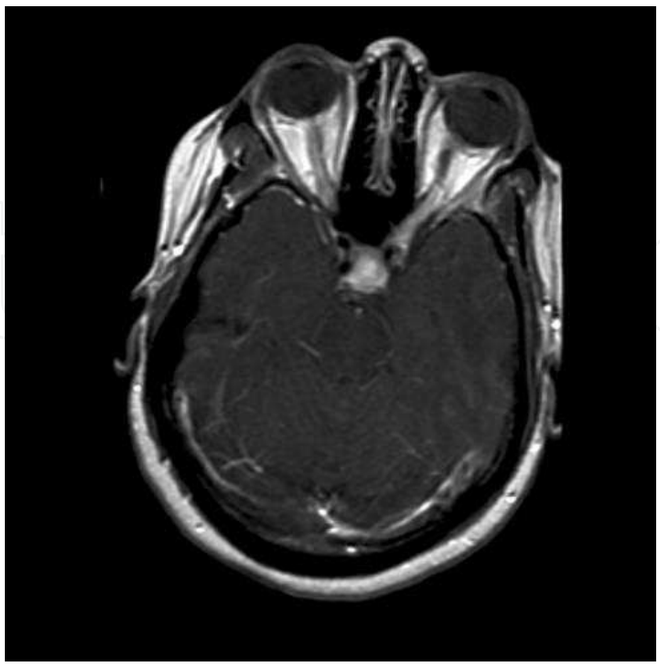


Fig. 2. Gadolinium enhanced MRI of the brain demonstrating bilateral optic nerve and pituitary axis enhancement

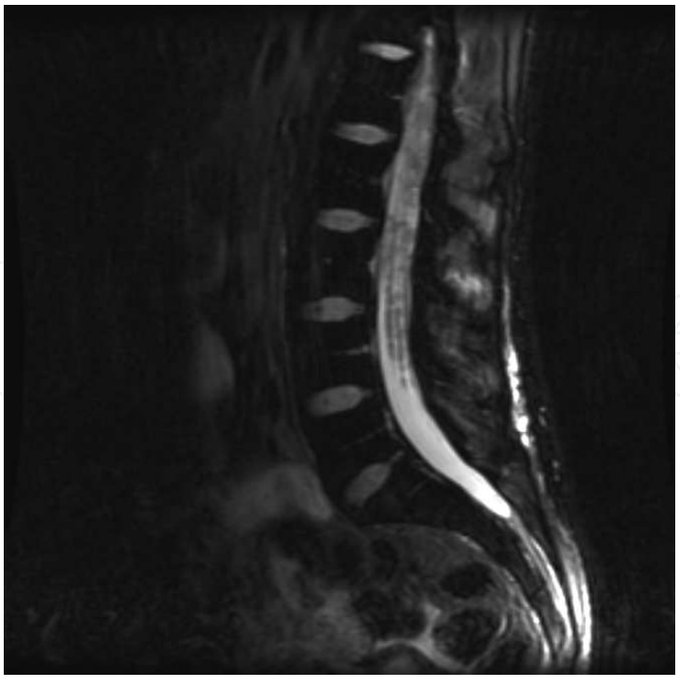


Fig. 3. MRI of the lumbosacral spine demonstrating diffuse radicular nodularity



Fig. 4. Gadolinium enhanced MRI of the thoracic spine demonstrating scattered nodular enhancement.

Spinal fluid evaluation is indicated for all patients suspected of having neurosarcoidosis, assuming that there is not a risk for herniation based on CNS imaging. Cerebrospinal fluid evaluation serves two purposes. First, it has a high sensitivity for demonstrating abnormalities in patients with neurosarcoidosis, even if they are relatively nonspecific. In addition, spinal fluid studies may be sent to help rule out other mimicking conditions of this disorder, such as infectious and malignant causes.

Neurosarcoidosis reviews (Aksamit and Norona 1999, Zajicek et al 1999) offer insight into the details of cerebrospinal fluid findings. The cerebrospinal fluid protein is typically elevated in roughly 70 to 80% of patients. The value may be very highly elevated and an average case would be above 100. Spinal fluid pleocytosis is seen in 55-72% of patients with a mean value of around 50, but values of several hundred can be seen. This is typically a lymphocytosis. Oligoclonal bands are positive in around 20% of patients. An elevated protein typically accompanies this, which might lead one to consideration of sarcoidosis, rather than a more typical multiple sclerosis case. Cerebrospinal fluid ACE levels are positive in only about 1/4 to 1/3 of patients. This low sensitivity is also coupled with concerns of specificity. Five of nine elevated cerebrospinal fluid ACE levels in the Mayo Clinic review were related to infectious or carcinomatous meningitis (Aksamit and Norona 1999).

Serum ACE levels have a relatively high sensitivity for undiagnosed sarcoidosis patients in general, and may approach 75% (Studdy and Bird 1989). Observations for patients presenting with neurosarcoidosis demonstrate potentially lower sensitivities overall with Joseph and Scolding (2009) having data of only a 29% positivity rate. This is likely due to many patients having a more localized expression of sarcoidosis in the nervous system. In addition, this test also suffers from specificity limitations with false positives in 2-4% of

normals and high false positive rates in patients with infection, liver disease, renal disease, hyperthyroidism, Gaucher's, and some cases of other disorders (Wallach 2000).

Around 90% of sarcoidosis patients have pulmonary involvement (Baughman 2004); nevertheless, due to the potentially more isolated disease of neurosarcoidosis, those numbers are not as high in series of patients presenting with neurological complications. Regardless, 50-60% of patients still had abnormalities and so this is still a very useful screening method in patients with a possible diagnosis of neurosarcoidosis (Pawate et al 2009, Joseph and Scolding 2009). Chest CT can enhance the sensitivity of pertinent findings, though in Pawate's series, only two patients with a normal chest x-ray had chest CT findings. This demonstrated that even a routine chest x-ray is a very useful initial screening measure (Pawate et al 2009). Gallium scanning can demonstrate characteristic uptake patterns in sarcoidosis, including the lung and parotid regions, for example, and informative abnormalities appear to be present in roughly half of patients presenting with neurosarcoidosis (Zajicek et al 1999, Joseph and Scolding 2009).

Taking into account all of the diagnostic information noted above, the main purpose is to guide the decision of whether to obtain a biopsy for suspicion of neurosarcoidosis, as well as to rule out other mimicking conditions. This confirmatory strategy is necessary in order to proceed with aggressive immunomodulatory medication. If there is evidence of systemic disease, then biopsy of the appropriate lung (transbronchial), skin, or lymph node tissue would be an appropriate strategy (Aksamit and Norana 1999, Aksamit 2008, Pawate et al 2009). In patients without this possibility, biopsy of a clinically relevant nervous system lesion, such as an enhancing area of the meninges or accessible significant parenchymal lesion could be considered for a definitive diagnosis (Aksamit 2008). Peripheral nervous system involvement could be biopsied, as well, with symptomatology and exam findings helping to guide that decision. A muscle biopsy could be considered even in patients without muscle related symptoms as 50% of patients have abnormalities on a muscle biopsy, which is well above the clinical incidence of muscle involvement (Delaney 1977). Other biopsy approaches of "clinically silent" areas would include a bone marrow biopsy or a conjunctival biopsy, which have a 30-40% chance of a positive result (Aksamit and Norona 1999). A conjunctival biopsy was recommended as an initial strategy by Aksamit due to its relatively non-invasive nature and question of whether the yield of muscle biopsy is as high as mentioned above (Aksamit 2008).

4. Treatment

Neurological involvement of sarcoidosis is, by definition, an indication for the initiation of medical treatment (Hunninghake et al 1999). The first line therapy is oral corticosteroids (Selroos 1994). For neurological disease, prednisone is to be started at around 1 mg per kilogram per day and continued for 6-8 weeks of high-dose therapy before beginning a very slow taper (Hoitsma et al 2004). Overall, treatment is suggested for last at least 6-12 months to help avoid progression or relapse of the disease (Aksamit 2008). Exceptions to this could include more benign or monophasic expressions of neurosarcoidosis, such as isolated Bell's palsy or aseptic meningitis, potentially being treated on the order of weeks rather than more chronically, given the favorable prognosis (Luke et al 1987). Along those lines the general rule is central nervous system disease, especially with significant parenchymal involvement or seizure activity, is more likely to have a poor prognosis and require more aggressive treatment than peripheral nervous system disease (Ferriby et al

2001, Stern et al 1985, Luke et al 1987, Scott 1993, Zajicek et al 1999). With more significant disease, not only is at least 6-12 months of corticosteroid treatment indicated, but steroid sparing agents may be necessary in cases that appear more likely to run a refractory course during the steroid taper or if the patient is not tolerating steroid treatment. Some options include methotrexate, cyclosporin, azathioprine, cellcept, or cytoxan (Androdias et al 2011, Agbogu et al 1995, Stern et al 1992, Soriano et al 1990, Elkin and Willcox 1985). These medications will likely need to be continued for 6-12 months or longer with significant disease. With severe disease onset, a pulse of IV methylprednisolone for 5 days before starting oral corticosteroids might be necessary, and, in addition, a steroid sparing agent might need to be started early in the course of therapy (Scott et al 2007). Management of corticosteroids and the immunosuppressants outlined above should be undertaken by a clinician who is familiar with these medications and their practice. Further details of the dosing and possible toxicity are similar to the general treatment principles with systemic disease. Finally, hydroxychloroquine is a medication that inhibits antigen presentation to MHC peptide complexes and their transport to the cell surface (Moller 2003). This medication theoretically could be considered as an add-on medication with an additional mechanism of action to treat sarcoidosis, but does not have much efficacy in the primary treatment of neurosarcoidosis. It may be beneficial in helping to maintain longer remissions in patients who have difficulty maintaining steroid remission without a relapse (Aksamit 2008). It is a well tolerated medication, though monitoring for retinal toxicity is necessary (Baughman and Lynch 2003). Finally, radiation therapy has been utilized in patients refractory to all medication therapy as a last resort (Bruns et al 2004, Menninger et al 2003).

Unfortunately, despite the treatment approach outlined above, patients with neurosarcoidosis can be steroid resistant and another 20-40% of those further resistant to the use of conventional immunosuppressive agents (Hoitsma et al 2004). The rationale for utilizing these treatments is to generically suppress the inflammatory response generated by a TH 1 mediated reaction to the antigen stimulus of sarcoidosis. The TH 1 mediated response to MHC-II complexes formed from antigen stimuli in sarcoidosis heavily involves interleukin-2, interleukin-12, interferon-γ, and tumor necrosis factor-α (Moller 2003). Tumor necrosis factor-α is the main cytokine of interest, and there have been several clinical trials of direct therapy to block it with encouraging results. The predominant examples of this include infliximab and thalidomide. Infliximab is a monoclonal antibody that blocks tumor necrosis factor-α. Concerns of infection related to immunosuppression, cytopenias, a paradoxical provocation of multiple sclerosis, allergic reactions, and significant cost of the medication are all factors that could limit its use. Nevertheless, there is a large and growing support for its efficacy, though lacking any confirmatory prospective study. Its use may be considered in patients refractory to other medical treatment (Pereira et al 2011, Santos et al 2010, Aksamit 2008). Likewise, thalidomide also has properties that involve tumor necrosis factor-α blockade. This medication is most known for its concerns for teratogenic effects, such as phocomelia, and it now has to be prescribed through the system for thalidomide education and prescribed safety (STEPS), only available to be prescribed through select physicians. In addition, toxicity such as an axonal sensory polyneuropathy develops in about 20% of patients. Sedation is the main limitation of the medication otherwise, which is very slowly titrated as tolerated from 100 mg to a max of 800 mg as needed (though typically 400 mg or less for maintenance). Other side effects could include rash,

thromboembolism, dizziness, and constipation. (Wu et al 2005) In contrast to other immunosuppressive therapies, there is not a significantly increased risk of infection with patients on thalidomide (Baughman and Lower 2004). Our experience is consistent with other authors, and demonstrates the efficacy of thalidomide in patients with steroid and immunosuppressant-refractory neurosarcoidosis (Hoyle, Newton, Katz 2008, Hammond et al 2007, Nguyen et al 2004).

The future trends in therapy will likely involve the use of drugs targeted to the underlying pathophysiology of sarcoidosis, such as the new tumor necrosis factor-α inhibitors currently under investigation. Also, future prevention or possible treatment of neurosarcoidosis could be enhanced by a better understanding of the antigen responsible for initiating sarcoidosis, and why such a small percentage of patients develop neurological involvement. Proprionibacterium and mycobacterium have been two antigenic candidates that have not resulted in any significant disease modification with attempts at treatment. Other environmental antigens have been proposed, as well. Further exploration of the antigenic source of initiation of sarcoidosis, the conditions that allow the host response to become susceptible to the development of non-caseating granulomas and, more specifically, how this can selectively occur in the nervous system will hopefully yield progress in the field.

5. Conclusion

Neurosarcoidosis is a complex disorder that may involve virtually any aspect of the nervous system. Nevertheless, it may present with certain classical features, such as cranial nerve involvement, meningeal based disease, or hypothalamic-pituitary axis symptomatology to alert one to the possibility of this diagnosis. Seizures, spinal cord involvement, encephalopathy/psychiatric symptomatology, and peripheral neuropathy occur with intermediate frequencies and less specificity for suspecting this condition, but need to be understood in the context of other clues systemically or otherwise to the disorder.

Diagnosis in cases of known systemic sarcoidosis is more straightforward, but in the absence of systemic features on presentation, diagnosis may be complicated. MRI of the brain with contrast (and potentially spinal cord) and cerebrospinal fluid studies are mandatory in the initial evaluation to not only demonstrate features suggesting a need to pursue a pathological tissue diagnosis, but also important in evaluating for other mimickers of the disease, chief among those being infection or malignancy. ACE levels have relatively poor sensitivity and specificity, but can increase suspicion of the disorder in cases without other apparent clues. A detailed clinical understanding of the features of systemic disease is important background knowledge for evaluating patients with potential neurosarcoidosis. Routine chest imaging and potentially gallium studies if needed can be helpful noninvasive adjuncts. Nevertheless, tissue diagnosis remains the gold standard and is necessary before committing to significant immunomodulatory therapy.

Corticosteroids remain the first-line therapy of neurosarcoidosis with steroid sparing agents reserved for more severe or refractory disease, or for patients who are intolerant to corticosteroids. Selective therapy of downstream inflammatory features of sarcoidosis, such

as with tumor necrosis factor-α antagonists, are becoming more recognized as options in refractory disease. Further exploration of targeted immunomodulatory therapy, better understanding of the antigenic initiation of the disease, and discovery of host factors that make one susceptible not only to sarcoidosis, but specifically nervous system involvement, are important areas for future progress in treating this disorder.

6. References

Agbogu BN, Stern BJ, Sewell C, Yang G. Arch Neurol. Therapeutic considerations in patients with refractory neurosarcoidosis. 1995 Sep;52(9):875-9.

Aksamit AJ, Norona F. Neurosarcoidosis without systemic sarcoid. Ann Neurol 1999;46:471.

Aksamit. Neurosarcoidosis. Continuum. 2008;14(1):181-196.

Alon EE, Ekbom DC. Neurosarcoidosis affecting the vagus nerve. Ann Otol Rhinol Laryngol. 2010 Sep;119(9):641-5.

Androdias G, Maillet D, Marignier R, Pinède L, Confavreux C, Broussolle C, Vukusic S, Sève P. Mycophenolate mofetil may be effective in CNS sarcoidosis but not in sarcoid myopathy.Neurology. 2011 Mar 29;76(13):1168-72.

Armin A, Balderacchi JL. Trigeminal neurosarcoidosis: case report and literature review. Ear Nose Throat J. 2010 Jul;89(7):320-2.

Aubart FC, Quayoun M, Brauner M, Attali P, Kambouchner M, Valeyre D, Nunes H. Sinonasal involvement in sarcoidosis: a case-control study of 20 patients. 2006 Nov;85(6):365-71.

Baughman RP. Pulmonary sarcoidosis. Clin Chest Med. 2004;25(3):521.

Baughman RP, Lower EE: Newer therapies for cutaneous sarcoidosis – the role of thalidomide and other agents. Am J Clin Derm 2004, 5(6):385-94.

Baughman RP, Lynch JP. Difficult treatment issues in sarcoidosis. Journal of Internal Medicine. 2003;253;41-45.

Bona JR, Fackler SM, Fendley MJ, Nemeroff CB. Neurosarcoidosis as a cause of refractory psychosis: a complicated case report. Am J Psychiatry. 1998 Aug; 155 (8): 1106 -8.

Bruns F, Pruemer B, Haverkamp U, Fischedick AR. Neurosarcoidosis: an unusual indication for radiotherapy. Br J Radiol 2004 Sep; 77(921):777-9.

Burns TM, Dyck PJ, Aksamit AJ, Dyck PJ. The natural history and long-term outcome of 57 limb sarcoidosis neuropathy cases. J Neurol Sci. 2006 May 15; 244 (1-2):77-87.

Chapelon C, Ziza JM, Piette JC, et al. Neurosarcoidosis: signs course and treatment in 35 confirmed cases. Medicine 1990;69:261-76

Christoforidis GA, Spickler EM, Reccio MV, Mehta BM. MR of CNS sarcoidosis: correlation of imaging features to clinical symptoms and response to treatment. AJNR1999; 20:655 –669

Colover J. Sarcoidosis with involvement of the nervous system. Brain 1948; 71:451-75.

De Mulder D, Vandenberghe J. Neurosarcoidosis as a cause of manic psychosis.Tijdschr Psychiatr. 2008;50(11):741-5. Dutch.

Delaney P. Neurologic manifestations in sarcoidosis: review of literature, with a report of 23 cases. Ann Intern Med 1977;87(3):336-45.

Elkin R, Willcox PA. Neurosarcoidosis. A report of 5 cases. S Afr Med J. 1985 Jun 8;67(23):943-6.

Fahoum F, Drory VE, Issakov J, Neufeld MY. Neurosarcoidosis presenting as Guillain-Barre like syndrome. A case report and review of the literature. J Clin Neuromuscul Dis. 2009 Sep;11(1):35-43.

Ferriby D, de Seze J, Stojkovic, T, Hachulla E, Wallaert B, Destee A, Hatron PY, Vermersch P. Long-term follow-up of neurosarcoidosis. Neurology 2001;57;927-929.

Friedman SH, Gould DJ. Neurosarcoidosis presenting as psychosis and dementia: a case report.Int J Psychiatry Med. 2002;32(4):401-3.

Garg S, Wright A, Reichwein R, Boyer P, Towfighi J, Kothari MJ. Mononeuritis multiplex secondary to sarcoidosis.Clin Neurol Neurosurg. 2005 Feb;107(2):140-3.

Gilmore K, Rudden M, Kalman TP. Psychiatric manifestations of sarcoidosis. Can J Psychiatry 1980;25:329-31.

Hammond ER, Kaplin AI, Kerr DA. Thalidomide for acute treatment of neurosarcoidosis. Spinal Cord 2007;45(12):802-3.

Heerfordt CF. Uber eine "Febris uveo-parotidea subchronica" an der glandula parotis und der uvea des anges lokalisiert und haufig mit paresen cerebrospinaler nerven kompliaiert. V Graef Arch Klin Exp Ophthalmol 1909;70:254.

Hoitsma E, Faber CG, Drent M, Sharma OP: Neurosarcoidosis: a clinical dilemma. Lancet Neurol 2004, 3(7):397-407.

Hoitsma E, Marziniak M, Faber GC, Reulen JP, Sommer C, De Baets M, Drent M. Small fibre neuropathy in sarcoidosis. Lancet 359 (2002), pp 2085-2086.

Hoyle JC, Newton HB, Katz S. Prognosis of refractory neurosarcoidosis altered by thalidomide: a case report. Journal of Medical Case Reports 2008, 2:27

Hunninghake GW, Costabel U, Ando M, Baughman R, Cordier JF, du Bois R, Eklund A, Kitaichi M, Lynch J, Rizzato G, Rose C, Selroos O, Semenzato G, Sharma OP: ATS/ERS/WASOG Statement Sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 1999, 16:149-173.

Joseph FG, Scolding NJ. Neurosarcoidosis: A study of 30 new cases. Neurol Neurosurg Psychiatry 2009 Mar;80(3):297-304.

Joseph FG, Scolding NJ. Sarcoidosis of the nervous system. Pract Neurol 2007;7:234-244.

Junger SS, Stern BJ, Levine SR, Sipos E, Marti-Masso JF. Intramedullary spinal sarcoidosis: Clinical and magnetic resonance imaging characteristics. Neurology 1993; 43: 333-337.

Luke RA, Stern BJ, Krumholz A, Johns CJ. Neurosarcoidosis: the long-term clinical course. Neurology 1987 Mar;37(3):461-3.

Menninger MD, Amdur RJ, Marcus RB Jr. Am J Clin Oncol 2003 Aug;26(4):e115-8.

Moller DR: Treatment of sarcoidosis – from a basic science point of view. Journal of Internal Medicine 2003, 253:31-40.

Nguyen YT, Dupuy A, Cordoliani F, Vignon-Pennamen MD, Lebbe C, Morel, P, Rybojad M. Treatment of cutaneous sarcoidosis with thalidomide. J Am Acad Dermatol 2004;50:235-241.

Niemer GW, Bolster MB, Buxbaum L, Judson MA. Carpal tunnel syndrome in sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 2001;18(3):296.

O'Brien GM, Baughman RP, Broderick JP, Arnold L, Lower EE. Paranoid psychosis due to neurosarcoidosis. Sarcoidosis. 1994 Mar;11(1):34-6.

Oksanen V. Neurosarcoidosis: clinical presentations and course in 50 patients. Acta Med Scand 1986;73:283-90.

Pawate S, Moses H, Sriram S. Presentations and outcomes of neurosarcoidosis: a study of 54 cases.QJM. 2009 Jul;102(7):449-60.

Pereira J, Anderson NE, McAuley D, Bergin P, Kilfoyle D, Fink J. Medically refractory neurosarcoidosis treated with infliximab. Intern Med J 2011 Apr;41(4):354-7.

Porter N, Beynon HL, Randeva HS. Endocrine and reproductive manifestations of sarcoidosis. QJM. 2003 Aug;96(8):553-61.

Sabaawi M, Gutierrez-Nunez J, Fragala MR. Neurosarcoidosis presenting as schizophreniform disorder. Int J Psychiatry Med. 1992;22(3):269-74.

Santos E, Shaunak S, Renowden S, Scolding NJ. Treatment of refractory neurosarcoidosis with infliximab. J Neurol Neurosurg Psychiatry. 2010 Mar;81(3):241-6.

Scott, TF. Neurosarcoidosis: Progress and clinical aspects. Neurology 1993;43:8-12.

Scott TF, Yandora K, Valeri A, Chieffe C, Schramke C. Aggressive therapy for neurosarcoidosis: long-term follow-up of 48 treated patients. Arch Neurol. 2007;64(5):691.

Selroos O. Treatment of sarcoidosis. Sarcoidosis 1994;11:80-83.

Sierra-Hidalgo F, Moreno-Ramos T, Martinez de Aragon A, Correas-Callero E, Erana I, de Pablo-Fernandez E. Longitudinal myelitis as the presenting symptom of neurosarcoidosis. Rev Neurol 2010 Sep 1;51(5):302.

Soriano FG, Caramelli P, Nitrini R, Rocha AS. Neurosarcoidosis: therapeutic success with methotrexate. Postgrad Med J. 1990 Feb;66(772):142-3.

Spiegel DR, Thomas CS, Shah P, Kent KD. A possible case of mixed mania due to neurosarcoidosis treated successfully with methylprednisolone and ziprasidone: another example of frontal-subcortical disinhibition?Gen Hosp Psychiatry. 2010 May-Jun;32(3):342.

Stern BJ, Krumholz A, Johns C, Scott P, Nissim J. Sarcoidosis and its neurological manifestations. Arch Neurol. 1985 Sep;42(9):909-17. Review.

Stern BJ, Schonfeld SA, Sewell C, Krumholz A, Scott P, Belendiuk G. The treatment of neurosarcoidosis with cyclosporine. Arch Neurol. 1992 Oct;49(10):1065-72.

Stuart C, Neelon F, Lebovitz H. Disordered control of thirst in hypothalamic-pituitary sarcoidosis. N Engl J Med 1980; 303:1078–82.

Studdy PR, Bird R. Serum angiotensin converting enzyme in sarcoidosis--its value in present clinical practice. Ann Clin Biochem. 1989;26 (Pt 1):13.

Tavee J, Culver D. Sarcoidosis and small fiber neuropathy. Curr Pain Headache Rep 2011 June;15(3):201-6.

Turkington RW, MacIndoe JH. Hyperprolactinemia in sarcoidosis. Ann Intern Med 1972;76(4):545-9.

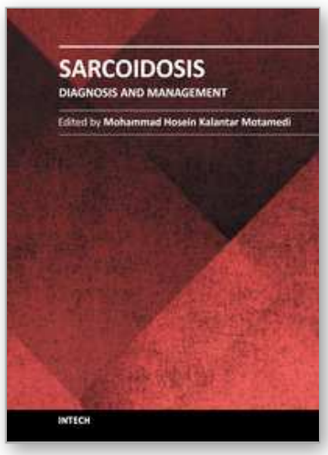
Wallach J. Interpretation of Diagnostic Tests, 7th Ed., 2000.

Wu JJ, Huang DB, Pang KR, Hsu S, Tyring SK: Thalidomide: dermatological indications, mechanisms of action and side-effects. British Journal of Dermatology 2005, 153:254-73.

Zajicek JP, Scolding NJ, Foster O, et al. Central nervous system sarcoidosis-diagnosis and management. QJM 1999;92(2):103-117.
Zuniga G, Ropper AH, Frank J. Sarcoid peripheral neuropathy. Neurology. 1991;41(10):1558.

IntechOpen

IntechOpen



Sarcoidosis Diagnosis and Management

Edited by Prof. Mohammad Hosein Kalantar Motamedi

ISBN 978-953-307-414-6
Hard cover, 280 pages
Publisher InTech
Published online 17, October, 2011
Published in print edition October, 2011

Sarcoidosis is a type of inflammation that occurs in various locations of the body for no known reason. Normally, when foreign substances or organisms enter the body, the immune system will fight back by activating an immune response. Inflammation is a normal part of this immune response, but it should subside once the foreign antigen is gone. In sarcoidosis, the inflammation persists, and some of the immune cells form abnormal clumps of tissue called granulomas. The disease can affect any organ in the body, but it is most likely to occur in the lungs. It can also affect the skin, eyes, liver, or lymph nodes. Although the cause of sarcoidosis is not known, research suggests that it may be due to an extreme immune response or extreme sensitivity to certain substances. It also seems to have a genetic component as well, and tends to run in families. Sarcoidosis most commonly develops in people between 20 and 50 years of age. African Americans are somewhat more likely to develop sarcoidosis than Caucasians, and females are somewhat more likely to develop sarcoidosis than males. The symptoms of sarcoidosis depend on the organ involved. This book deals with the diagnosis and treatment of this mysterious disease of unknown etiology.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

J. Chad Hoyle and Herbert B. Newton (2011). Neurological Sarcoidosis, Sarcoidosis Diagnosis and Management, Prof. Mohammad Hosein Kalantar Motamedi (Ed.), ISBN: 978-953-307-414-6, InTech, Available from: http://www.intechopen.com/books/sarcoidosis-diagnosis-and-management/neurological-sarcoidosis

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2011 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the Creative Commons Attribution 3.0 License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen