

Neurosarcoidosis: Clinical, Pathological and Therapeutic Issues

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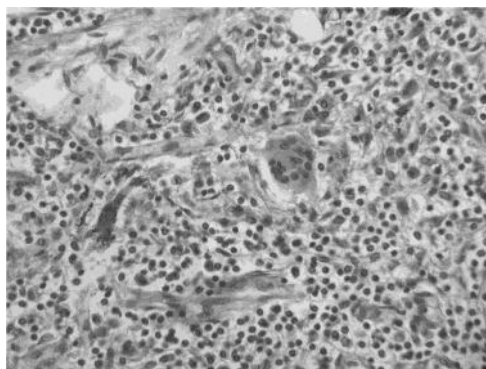
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This paper will describe the Johns Hopkins TM and MS Centers' experience regarding the clinical, pathological, and treatment issues related with neurosarcoidosis. Sarcoidosis is a multisystemic disease. It is important for us to understand Sarcoidosis, because when it affects the brain or the spinal cord, it mimics disorders like multiple sclerosis and transverse myelitis. We are trying to advise physicians that sarcoidosis is a disease that needs to be evaluated carefully before establishing a diagnosis of multiple sclerosis or transverse myelitis.

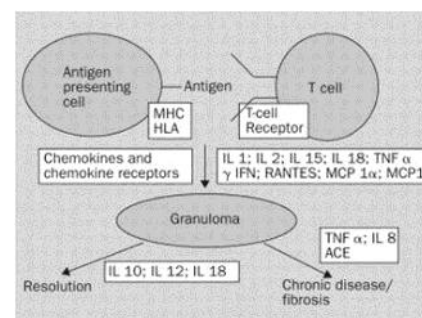
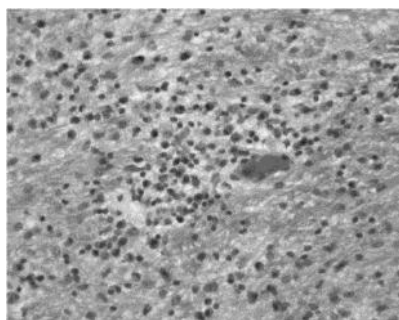
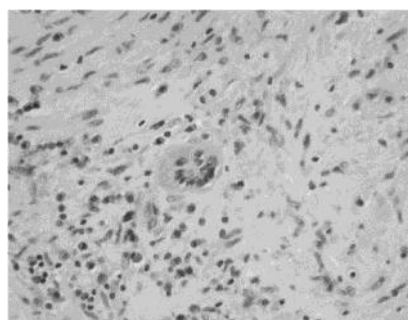
Sarcoidosis: Lung Granuloma



Sarcoidosis is a multisystemic granulomatous disorder. Multisystemic means that it may affect different parts of the body or different organs. It is primarily a disease that affects the lungs and the lymph nodes. The lymph nodes are intimately related with immunological function. The etiology is unknown; at present we do not know what causes this disease. It is a devastating disease in some patients that can produce a multitude of symptoms. Some of the symptoms include chronic coughing, malaise, episodic sweating and fever, fatigue, dyspnea and weight loss.

Sarcoidosis is frequently found when physicians are evaluating x-rays of the chest. Visualization of enlarged lymph nodes in the lungs leads to further assessment by tissue biopsy. Biopsies of the lymphatic tissue result in the identification of granulomas which are the hallmark of Sarcoidosis.

Sarcoidosis: Immune Response



There currently is no direct evidence regarding the factors that might cause Sarcoidosis. There is some speculation and experimental evidence, however, that Sarcoidosis may be an infectious disease caused by microorganisms. It is possible that persistent infections of bacteria may contribute to the symptoms seen in the lymph nodes and the lungs.

It is very well known that there is some type of genetic susceptibility to Sarcoidosis. It has been demonstrated that there are populations that have major histocompatibility complex (MHC) markers that are associated with a high risk of this disorder and populations that have markers that are associated with a low risk for this disorder. It is also known that polymorphisms in the cytokine family of genes may be involved in genetic susceptibility.

Sarcoidosis: Epidemiology

• **Etiological factors:**

- Mycobacteria
(19 studies, 0%-89% positivity rate)
- *Propionibacterium acnes*
- *Propionibacterium granulosum*

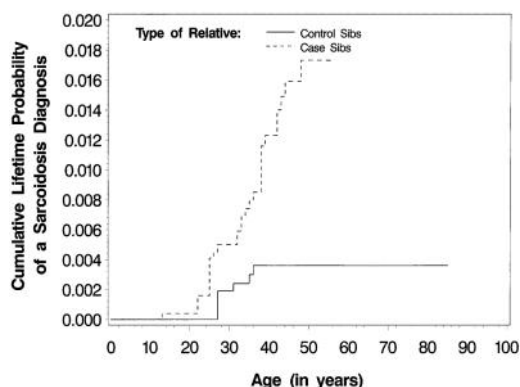
• **Genetic susceptibility**

- MHC
 - ⊙ Risk (HLA DR 11,12,14,15,17)
 - ⊙ Risk (HLA Dr1, DR4, DQ*0202?)
- TNF α (The -308)
- ACE (intron 16, -267)

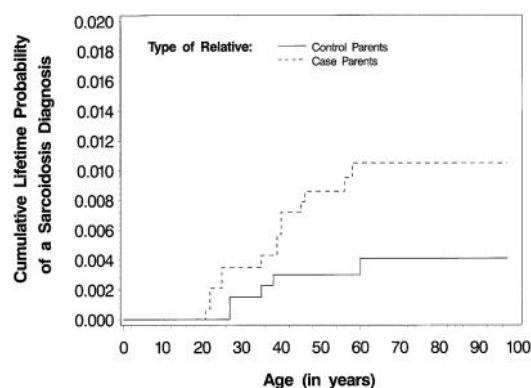
In the southeast and northeast United States, there are increased numbers of patients with sarcoidosis. Sarcoidosis has also been found to be more prevalent among the African-American population and among Caucasians of Nordic ancestry. We don't understand the increased prevalence of sarcoidosis in these populations, and that raises some concerns about potential issues like en-

vironmental risk or the presence of some familial clustering of sarcoidosis.

Risk of Sarcoidosis in Siblings (ACCESS study) Source: ACCESS Study, Am J Respir Crit Care Med 164:1885, 2001

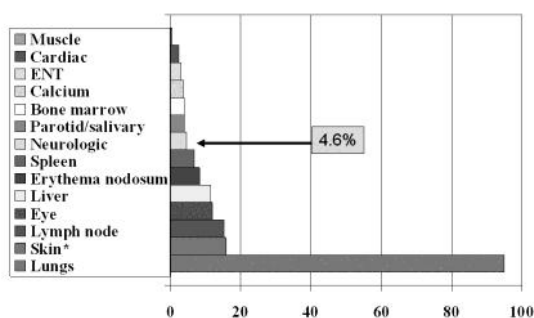


Risk of Sarcoidosis in Parents (ACCESS study) Source: ACCESS Study, Am J Respir Crit Care Med 164:1885, 2001



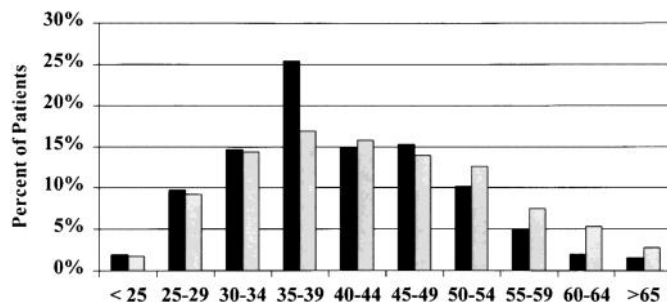
There is a very large longitudinal study on sarcoidosis that was done at the end of the 1990's and was completed in early 2000. The study demonstrated that there is a cumulative risk of sarcoidosis in relatives of patients that have suffered the disease. Interestingly, there is also a potential of sarcoidosis cases in parents of people that have been affected with this disorder.

Sarcoidosis: Organ Involvement (ACCESS: 736 patients 1997 – 1999) Source: ACCESS Study, Am J Respir Crit Care Med 164:1885, 2001

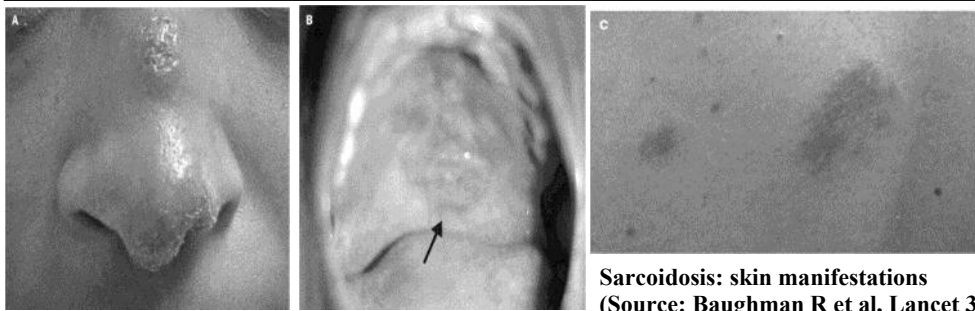


This graphic depicts the group of patients in the ACCESS sarcoidosis study, the largest longitudinal study of sarcoidosis that has been done in the United States, and the population that may be at risk for neurological problems. Neurological involvement was found in 4.6% of the overall population, which is not a high percentage, but the neurological involvement was very aggressive and produced a lot of disability due to the presence of spinal cord involvement, or peripheral nerve involvement, or encephalitis. The graphic makes clear that while Sarcoidosis predominantly affects the respiratory system, it can impact all the areas of the body, including the skin, eyes, liver, and many other organs. This is the reason we call Sarcoidosis a multi-systemic disorder.

Sarcoidosis: Age and sex at diagnosis (ACCESS: 736 patients 1997 – 1999) Source: ACCESS Study, Am J Respir Crit Care Med 164:1885, 2001

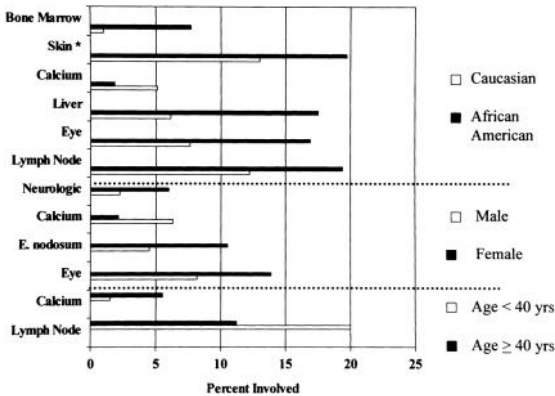


The main peak of onset is between 30 and 50 years of age. In this graphic, the black bar represents the female population and the gray bar is the male population. It can be seen that at peak ages there is a predominance of females impacted by Sarcoidosis.



These images show some of the manifestations of Sarcoidosis on the skin. Sarcoidosis may produce mucosa lesions and skin lesions that appear to be chronic. These lesions are one of the keys to the diagnosis of this disorder.

Sarcoidosis: skin manifestations
(Source: Baughman R et al, Lancet 361:1111; 2003)



Organ involvement – differences between groups: race, sex, age (ACCESS: 736 patients 1997 – 1999) Source: ACCESS Study, Am J Respir Crit Care Med 164:1885, 2001

It is interesting that despite the fact that the percentage of people with neurological symptoms from Sarcoidosis is relatively low (around 5 percent of this population), the female population is more affected by neurosarcoidosis as compared to the male population. The reasons for this susceptibility are not known.

- **Acute**
 - Skin: Erythema nodosum, MP rash
 - Acute iritis, conjunctivitis, nodules
 - Hilar adenopathy
 - Facial palsy
 - Hypercalcemia/calciuria
 - ACE ↑, Gallium +
- **Chronic**
 - Skin: Plaques, keloids, ulcers
 - Chronic uveitis, glaucoma, keratoconjunctivitis
 - Pulmonary infiltration
 - Multisystemic involvement
 - ACE →, Gallium +/-

Sarcoidosis: Clinical Approach (Acute and Chronic)

Sarcoidosis may manifest acutely, primarily with skin and ocular manifestations, or it may produce a chronic symptomatology that may involve different organs.

When a clinician sees a patient with suspected sarcoidosis, we do a very thorough evaluation. Since the main area of involvement is the lungs, a great deal of attention is focused on the respiratory system. There are different approaches used that allow us to detect areas of inflammation or the presence of enlarged lymph nodes. These approaches include chest X-Rays and CT scans, as well as nuclear medicine tests such as Gallium scans, and FDG PET-scans. There are also laboratory tests used for diagnosis, such as the use of angiotensin-converting enzyme (ACE) which can give useful information. In the 60’s and 70’s a skin test was introduced by European physicians called the Kveim-Siltzbach test, but this is no longer available in the United States, because of the potential risk of transferring infections.

Sarcoidosis: Diagnosis

- Clinical approach
- Radiology/Nuclear medicine:
 - Chest X-ray, Chest CT scan
 - Gallium scan
 - FDG PET scan
- Laboratory:
 - Angiotensin-converting enzyme (ACE)
 - Serum/Urine Calcium
- Skin test: Kveim-Siltzbach test

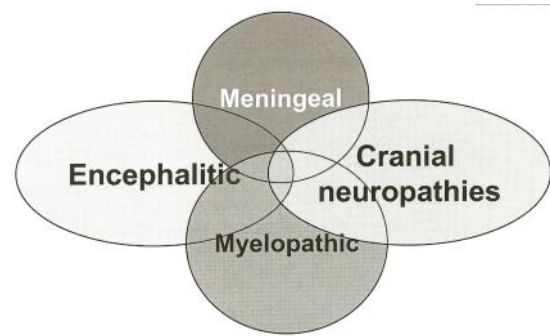
In summary, approximately 5 to 10 percent of patients with sarcoidosis may present with neurosarcoidosis. Interestingly, 50% of Neurosarcoidosis patients have neurological symptoms as the first manifestation of sarcoidosis. Any area of the central nervous system or peripheral nervous system may be affected. This is the reason we raise attention about Sarcoidosis; these patients may manifest with disorders that can mimic multiple sclerosis or mimic meningitis or mimic spinal cord involvement.

Historically, there have been a number of studies that demonstrate the multifocality of neurosarcoidosis in the central nervous system. Sarcoidosis may involve the presence of abnormal-

Clinical Involvement	Sharma 1997 (n=37)	Chapelon 1990 (n=35)	Stern 1985 (n=33)	Delaney 1977	Wiederholt 1965
Cranial neuropathy	52%	37%	73%	48%	64%
Aseptic meningitis	24%	40%	18%	26%	...
Hydrocephalus	...	40%	9%	17%	...
Hypothalamic	...		15%	26%	25%
Myelopathy	...		6%	9%	4%
Peripheral neuropath	24%/GBS 5%	40%	6%	4%	14%
Myopathy	8%	9%	12%	9%	7%

ities in cranial nerves (cranial neuropathy), such as optic neuritis or facial paralysis. Neurosarcoidosis may also manifest with meningitis or with other problems, such as hydrocephalous, hypothalamic dysfunction, or the presence of myelitis, myelopathies, or the presence of muscle involvement or peripheral nerve involvement. The statistics that have been published in the last 20 years demonstrate the multifocality of involvement of this disorder.

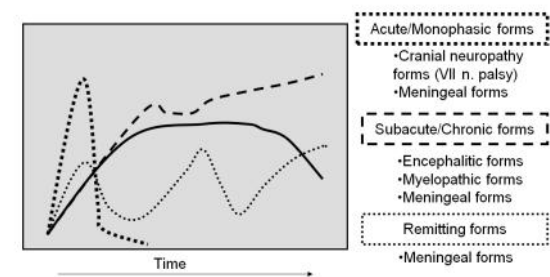
Neurosarcoidosis: Clinopathological Classification



Sarcoidosis is a disease that may affect any compartment of the central nervous system or peripheral nervous system. Patients may have problems associated with encephalitis, myelitis, or they may have problems associated with cranial nerve involvement.

The evolution of this disorder is quite variable. There is a subset of patients in which the primary manifestation of the disease is acute; just one episode of either cranial nerve involvement, or one episode of meningeal involvement (meningitis).

Neurocarcoidosis: Temporal profile



There are other patients for whom the course of the disease follows a temporal pattern that appears to be relapsing and remitting similar to an immunological disorder like multiple sclerosis. There are other groups of patients for whom there is a chronic progression of the disorder that produces a lot of disability and neurological problems.

In general, the most acute manifestation of the disease is the presence of cranial nerve involvement, such as facial paralysis, as Bell’s paralysis, or a form of acute meningitis. The chronic encephalitic or myelopathic forms are also frequent.

I am now going to present some examples of this disorder beginning with the meningeal manifestation. The meningeal involvement associated with sarcoidosis implies that you may have a patient in which there is aseptic meningitis, meaning that there is a chronic inflammation or acute inflammation that is not associated with bacterial infections or with viral infections.

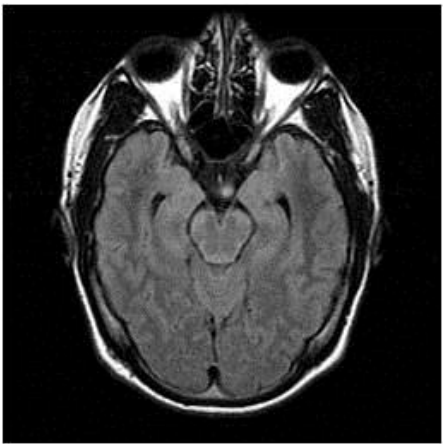
The patient may manifest with chronic meningitis, or recurrent meningitis. In very aggressive forms, the patient may manifest with a thickening of the dura mater or even the presence of tumor-like lesions of the dura mater that often mimic brain tumors. All of these manifestations and all of these inflammatory processes are going to produce a multitude of symptoms that go from presence of headache, presence of hydrocephalous, or even presence of other problems like cranial nerve paralysis and papilledema and visual loss.

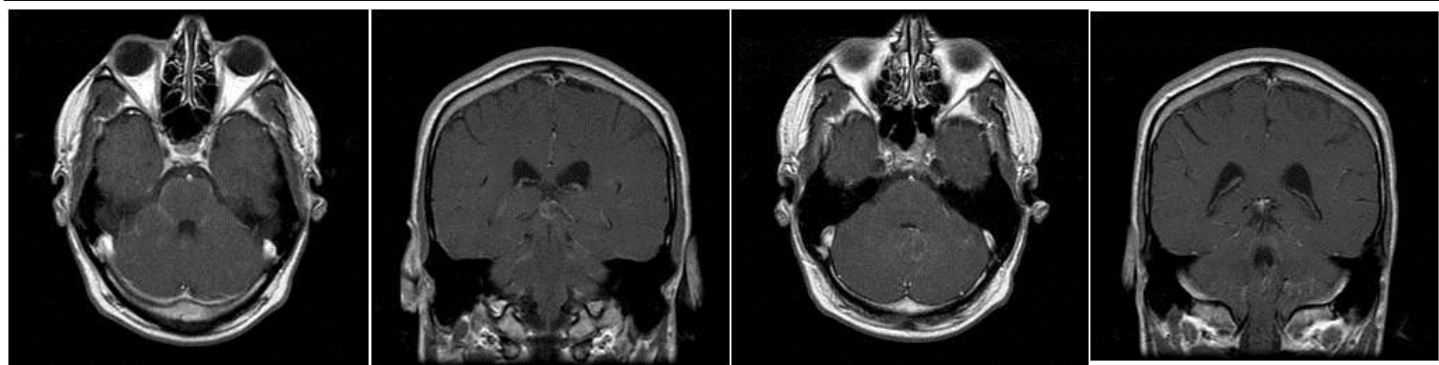
The brain MRI demonstrates that meningeal involvement means inflammation of the covering of the brain. There is enhancement of the leptomeninges; this is one of the manifestations of the disease. The enhanced white lines or the enhanced areas in which there is a patchiness, are a manifestation of the inflammatory process affecting the meninges.

Neurosarcoidosis: Clinical Classification (Meningeal forms)

	Neurological presentation	Clinical profile	Clinical course
Meningeal forms	•Aseptic meningitis •Basal meningitis Chronic meningitis/ •Pachymeningitis •Dural tumor-like sarcoid lesions	Headaches Increase intracranial pressure Hydrocephalus Papilledema Cranial nerve palsies, mono- or multiple	•Subacute •Relapsing-remitting •Chronic

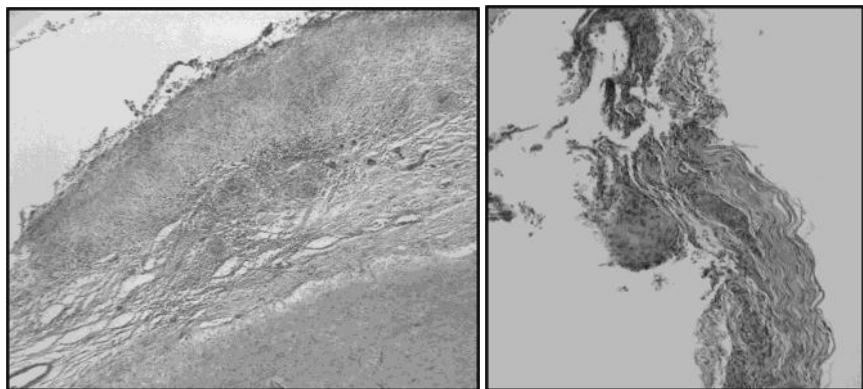
Meningeal MRI's





Meningeal Pathologies

Pathologically, this process is characterized by the presence of inflammation. Inflammation is going to produce infiltration by white cells in the meninges, and is going to produce the presence of granulomas that are the most important hallmark of this disorder.



Neurosarcoidosis: Clinical Classification
(Cranial neuropathies)

	Neurological presentation	Clinical profile	Clinical course
Cranial neuropathies	• Facial paralysis • Optic neuropathy • Multiple cranial neuropathies	Mono- or multiple cranial nerve palsies Bilateral Bell's palsy Diplopia Visual blurriness Vestibular symptoms	• Acute • Subacute, • Monophasic • Relapsing-remitting

Cranial neuropathies are another group of manifestations of neurosarcoidosis. These manifestations of the disease are going to affect different cranial nerves, such as the optic nerve or the facial nerve. Cranial neuropathies may produce symptoms such as visual loss or muscle dysfunction. The cranial neuropathies may have different temporal manifestations from acute to sub acute to chronic.

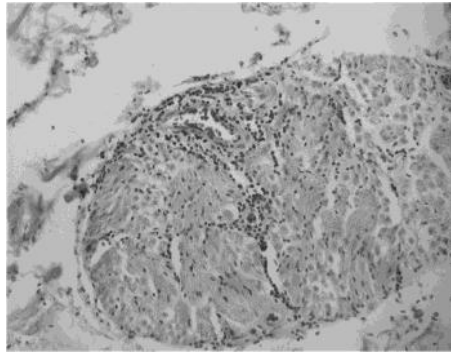
We frequently observe the association of both cranial neuropathy and meningitis. Meningitis may involve the brain stem which would contribute to cranial nerve involvement and subsequent cranial nerve paralysis.

Cranial neuropathy pathology



Graphic Neurosarcoidosis Cranial Nerve Involvement+MRI
Series A: Stern et al, 1986 Series B: Chapelon et al, 1990

	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII
A 33	3	3	2	1	3	3	11/	1/	1			1
B 35			4		5	2	11	1	1	2	2	2



Endoneurial and perineurial Inflammation

- ◆ Ischemic neuropathy
- ◆ Axonopathy
- ◆ Myelin loss

Pathologically, when a cranial nerve is affected, the major impact involves inflammation. This image is from a pathological study from a patient that died after sarcoidosis. This is a cross section of a facial nerve and one may observe the infiltration of that cranial nerve by inflammatory cells.

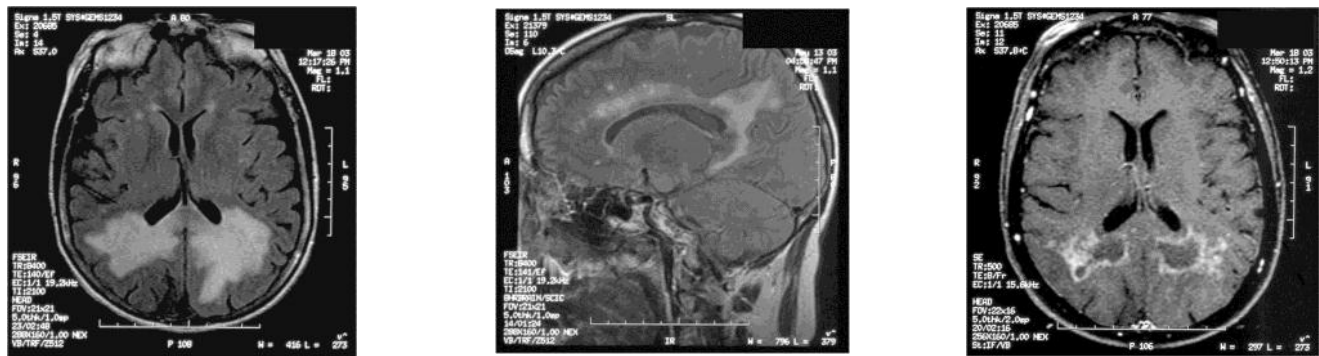
Neurosarcoidosis: Clinical Classification (Encephalitic forms)

	Neurological presentation	Clinical profile	Clinical course
Encephalitic forms	•Focal encephalitis •Focal or multifocal leukoencephalitis •Tumor-like sarcoid lesions	Headaches Psychosis Seizures Neuroendocrine manifestations Increased intracranial pressure Focal neurological symptoms	•Subacute •Relapsing-remitting •Chronic

One of the most aggressive manifestations of these disorders is the encephalitic form of the disease. The encephalitic form means that there is inflammation of the brain parenchyma; that is in contrast with other forms of the disease, in which the inflammation is predominantly the meninges, the covering of the brain. These forms may affect white matter, grey matter or it may produce tumor-like lesions. These forms are going to produce complex manifestations such as headache, psychoses, seizure activity, endocrinological problems, and significant neurological disability. These are the forms that frequently mimic multiple sclerosis, thus, it is extremely important that patients with suspected multiple sclerosis be evaluated to be sure that

they do not have neurosarcoidosis. The temporal pattern of these types of manifestations is that the brain parenchyma may be affected in a relapsing-remitting or chronic profile; very similar to what happens in multiple sclerosis.

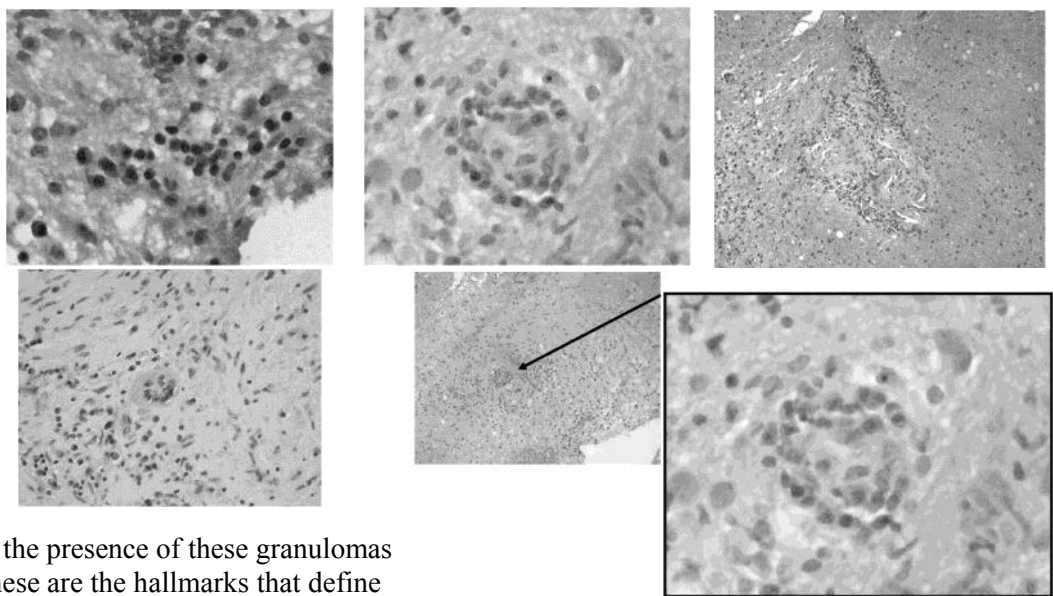
Neurosarcoidosis: Encephalitic form MRI's



These are very dramatic images of the brain of a patient affected by sarcoidosis. We recently evaluated this patient and there was extensive encephalitis predominantly affecting the white matter. Initially, there was concern about the presence of a brain tumor, like a glioblastoma multiform. For this reason, the patient got a biopsy and the surprise for us was that this was no tumor. The tissue biopsy confirmed that this was a manifestation of neurosarcoidosis.

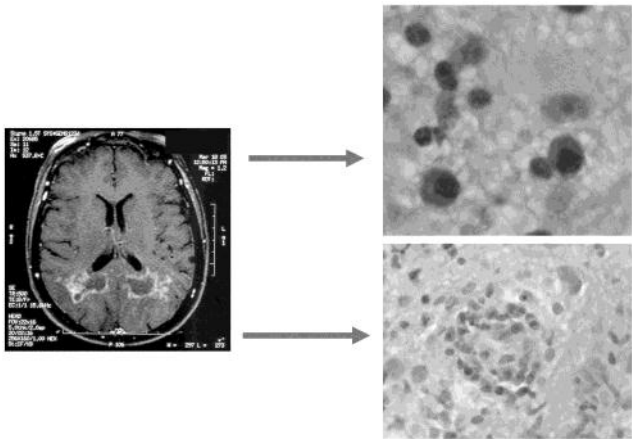
Neurosarcoidosis: Encephalitic forms: Pathological Features

- Lymphocytic infiltrates
- Plasmocytic infiltrates
- Perivascular cuffing
- Demyelination
- Gemistocytic astrocytes
- Parenchymal and leptomeningeal granulomas without necrosis
- Negative AFB staining



The tissue biopsy demonstrated the presence of these granulomas and inflammatory reactions. These are the hallmarks that define the neurosarcoidosis.

Conclusion: Granulomatous encephalitis = Neurosarcoidosis



In this particular case, what defined and concluded the overall clinical assessment is that this patient suffered from the encephalitic form of neurosarcoidosis. This was good news because we were able to treat the inflammation with the use of a steroid, IV Solumedrol. Subsequently, the patient received treatment with Prednisone, and is doing much better. During the follow-up investigation, we found that the patient also had sarcoidosis affecting her lungs.

Neurosarcoidosis: Clinical Classification (Myelopathic form)

	Neurological presentation	Clinical profile	Clinical course
Myelopathic form	Subacute or progressive myelopathy	Gait disturbances Paraparesis/ Paraplegia Bladder dysfunction Paresthesias/ dysesthesias Sensory level	Subacute, Monophasic, relapsing-remitting or chronic

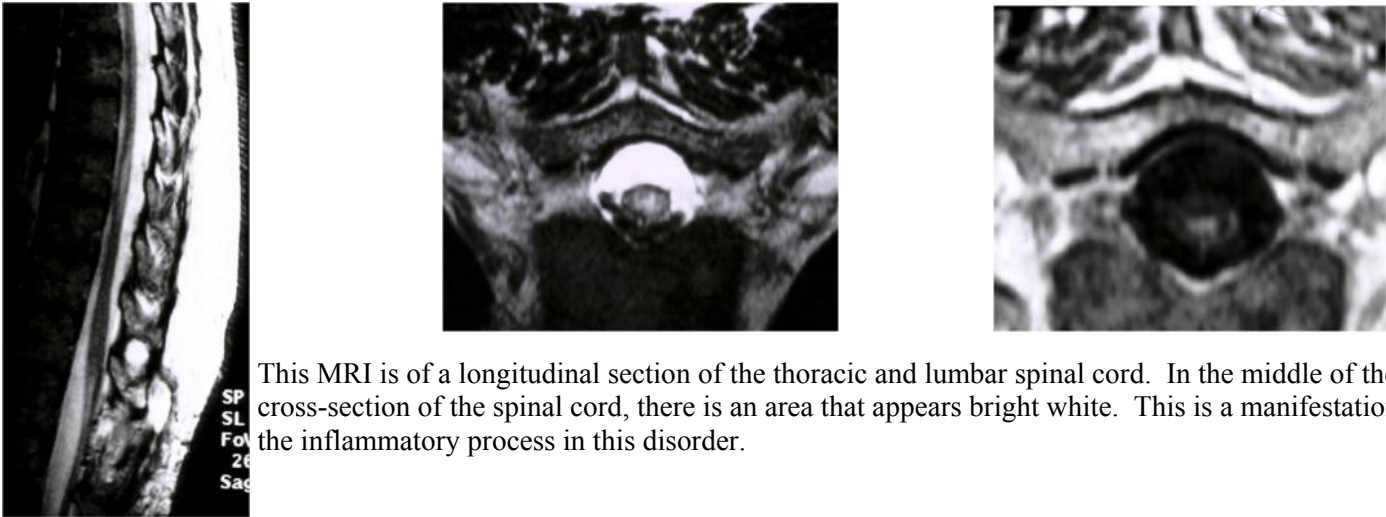
Patients with transverse myelitis also have to be evaluated for neurosarcoidosis. When there is a sub-acute form of myelitis or progressive myelopathy or chronic myelopathy, one of the concerns is the presence of sarcoidosis. We see this with relative frequency in patients with these types of temporal profiles. This is one of the issues in evaluating the differential diagnosis between myelopathy and neurosarcoidosis.

Neurosarcoidosis: Myelopathic form MRI's



Neurosarcoidosis in the spinal cord is very aggressive and produces a lot of spinal cord changes. This is a MRI of a patient affected by neurosarcoidosis. The inflammatory granuloma lesion is taking up a large portion of the spinal cord, and producing

significant clinical manifestations, such as paraparesis (weakness in the lower extremities) and sensory deficit.



This MRI is of a longitudinal section of the thoracic and lumbar spinal cord. In the middle of the cross-section of the spinal cord, there is an area that appears bright white. This is a manifestation of the inflammatory process in this disorder.

Neurosarcoidosis: Clinical Classification (peripheral nervous system)

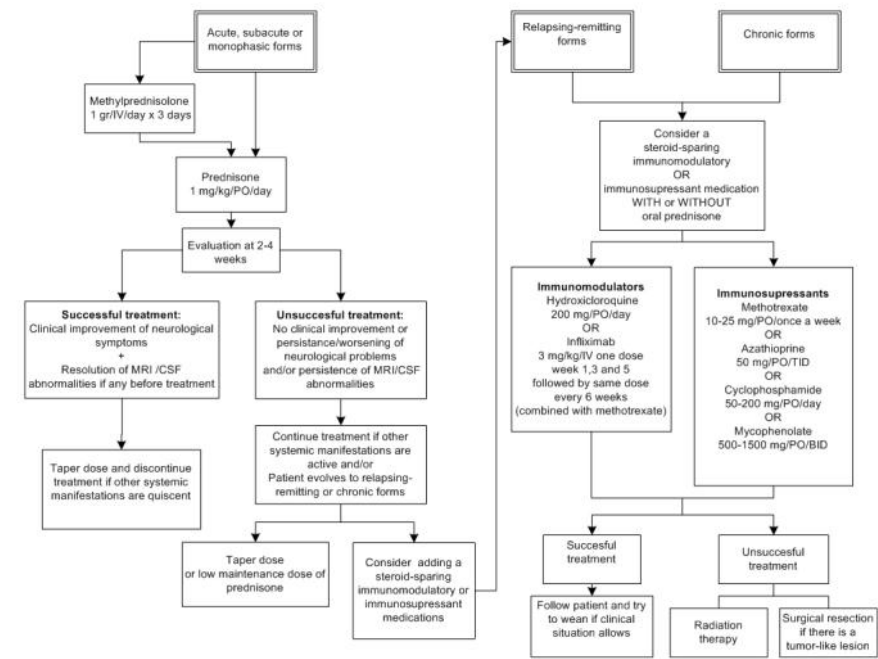
Clinical Forms of Neurosarcoidosis: Peripheral Nervous System			
	Neurological presentation	Clinical profile	Clinical course
Neuropathic form	Multiple mononeuropathies Polyradiculoneuropathies	Multifocal or localized dysesthesias, paresthesias, weakness, mono- or polyradiculopathies	Subacute, Relapsing-remitting or chronic
Myopathic forms	Focal myositis Polymyositis	Weakness, muscle pain	Acute, subacute or chronic. Occasionally indolent

Neurosarcoidosis may produce involvement of any part of the central nervous system, and it may also affect any part of the peripheral nervous system. It may affect the peripheral nerves or it may affect the muscle. This is going to be associated with significant manifestations of numbness, tingling, or the presence of muscle weakness.

This complex diagram identifies the treatment decisions for neurosarcoidosis. The treatment is divided into acute forms, the relapsing-remitting forms and the chronic forms of the disease. The acute treatment is based primarily on the use of IV Solumedrol or Methylprednisolone or Prednisone. These treatments are similar to what we use in patients with acute myelitis or patients with flare-ups of mul-

tipile sclerosis. In general terms, the treatment of all of these immunological disorders is very similar in many ways. However, when we complete the treatment of the acute manifestations, we need to decide if the patient needs chronic treatment or whether the treatment of the acute process was enough to control the disease. Unfortunately, in the majority of patients with neurosarcoidosis, we need to continue with chronic treatment. The chronic treatment is based on the use of immunomodulatory medication or the use of immunosuppressant medication. Immunosuppressant medications include Methotrexate, Azathioprine, Cyclophosphamide, or Mycophenolate. All of these medications help to control the inflammatory process which is one of the main mechanisms of the disease in neurosar-

coidosis.



There are recent treatment approaches that modulate the presence of some cytokines. The introduction of new medications has produced modulation of the antibody response in sarcoidosis or the reduction of the TNF associated production. All of these immunosuppressant approaches are very helpful in the control of the symptomatology.

The treatment of sarcoidosis depends on the clinical manifestation and the temporal profile. This is extremely important because there are encephalitic forms and myelopathic forms that require more aggressive treatment. This more aggressive treatment means not only the use of steroids, but also the use of immunosuppressant medications.

There are forms of sarcoidosis, for example acute forms, in which the use of steroids, such as Prednisone, is good enough to control the disease.

The temporal profile is also extremely important in deciding the type of treatment we are going to use. Whether it is a monofocal disease or a multifocal disease will determine how aggressive our treatment approach will be.

Treatments in women or in elderly people are another important consideration. The majority of approaches involve use of Prednisone or chronic use of steroids. This is very difficult in women that are post-menopausal, because of the high risk of problems associated with osteopenia or osteoporosis. We have to be careful that our treatment approach does not produce more harm than benefit.

In many patients, there is damage of the neuroendocrine function. This damage is produced by the involvement of the hypothalamus and pituitary gland. In these particular situations, the damage is going to produce chronic endocrinologi-

cal problems, such as hypothyroidism, hypogonadism, and other complex endocrinological processes. These problems will require treatment. These problems are not necessarily associated with active inflammation, but rather are the consequence of the damage to the hypothalamus or pituitary gland.

To conclude, Sarcoidosis is a multisystemic disease. It is immunologically mediated. We do not know the etiology of the disorder. In many ways, it appears to be a disorder that mimics a chronic infectious disorder, similar to what we see in tuberculosis. This is one of the reasons we are currently focusing on a search of potential etiological factors, such as micro bacterial infection.

Sarcoidosis is a very heterogeneous disease. Every patient with multiple sclerosis or with myelitis or myelopathies needs to be evaluated very carefully for sarcoidosis. This disease may mimic what we see in these disorders in the brain or in the spinal cord or peripheral nervous system. We are working hard on education about this disorder to get physicians who work in immunological problems and the NIH to pay more attention to this multisystemic disease.

We are trying to modify the standard of care. There are good studies which demonstrate that the CSF H-level is useless. A Mayo Clinic study has detailed that after extensive assessment of the spinal fluid in patients with sarcoidosis, the test was not necessarily reliable and there was no evidence of good sensitivity or good specificity. I think it is useless to request CSF H-level.

Chest X-rays may help, but unfortunately are not good enough. We are trying to encourage physicians who are evaluating sarcoidosis to first request a chest CT scan with contrast. A Gallium scan would be better but, unfortunately, is very expensive. A FDG PET-scan would be even better. The FDG's are flourodioxyglucose PET scans. This is a nuclear medicine-based test that allows us to assess inflammatory activity in different areas of the body. It is a very powerful technique. It is very expensive and the majority of insurance companies deny the use of this test for assessment of sarcoidosis. The cost is close to \$5000 versus a chest CT scan that is between \$700 and \$800. We are trying to tell the insurance company that if we diagnose sarcoidosis early, we can save a lot of money by avoiding more complications in patients. Investing four or five thousand dollars in the FDG PET scan is going to save money in the future. Not too many insurance companies are accepting this position.

If there is suspicion about sarcoidosis, if there is clinical evidence of something going on in the brain and the spinal cord, and if there is a suspicious chest CT scan, it is important to get a pulmonologist involved. They should get a lymph node biopsy or a lung biopsy. If it is demonstrated in a lymph node biopsy or a lung biopsy that there is sarcoidosis, then this patient very likely has neurosarcoidosis. It is very important to do a thorough assessment of the patient at the outset as opposed to giving treatment and then not following up on these other diagnoses. It is possible that the patient can be treated for the neurological problem with steroids or Prednisone, whether it is sarcoidosis or MS and then the opportunity may be missed to establish the definitive diagnosis.

We believe that almost 50 percent of patients with neurosarcoidosis have oligoclonal bands and have increased IgG index. In our pathological findings we have seen evidence of B-cell infiltration in the brain parenchyma or meninges; I think that is the reason we see oligoclonal bands and an IgG increase. We are currently doing this study, and it is not yet published in the literature. So unfortunately, that spinal fluid assessment is not going to help us too much in establishing a definite diagnosis of neurosarcoidosis. But, as I mentioned before, if you have a suspicious chest X-ray or chest CT-scan, you may have the opportunity to do a lymph node biopsy, or a bronchial lavage, or lung biopsy and see if the diagnosis can be established in that way.

I think that that's an approach, and that is absolutely required if the patient is an African-American patient, and you emphasize to the residents and everybody, you have an African-American patient, you are obligated to get a chest CT-scan for problems like optic neuritis, problems like uveitis, problems like encephalitis, meningitis, or anything that resembles sarcoidosis.

One thing we need to emphasize is the care of the patient with sarcoidosis is multi-disciplinary, we need to get the pulmonologist involved, we need to get the endocrinologist involved, because those patients are going to have a lot of problems related to those areas of medicine. Patients are going to have opthamological problems as well, or a patient may have a lot of cardiomyopathies because sarcoidosis also affects the heart and produces difficult problems with cardiomyopathies.
