Neurosarcoidosis

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Patient Education Session

Jeffrey M. Gelfand, MD
Assistant Professor of Clinical Neurology
UCSF MS Center, Dept of Neurology
University of California, San Francisco

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Sarcoidosis

- Inflammatory disorder of unclear cause characterized by “non-caseating granulomas” (under the microscope)

- The nervous system (brain, spinal cord, and nerves) is thought to be directly affected in 5-15% of patients with sarcoidosis

- But not all neurological problems in people with sarcoidosis are necessarily “neurosarcoidosis”
Neurological symptoms in people with sarcoidosis could...

1) Have nothing at all to due with sarcoidosis

2) Be caused directly by the granulomatous inflammatory process of sarcoidosis (“Neurosarcoidosis”)

3) Be a consequence of having sarcoidosis, but not due to active granulomatous inflammation at the site of nervous system injury (Neurological symptoms secondary to having sarcoidosis, but not “neurosarcoidosis”)

4) Be a complication of therapy or the immunological alterations of sarcoidosis (infection, medication side effect, other complication)
Neurological Symptoms are Common in People with Sarcoidosis: 
*Data from the UCSF Sarcoidosis Research Program*

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Unaffected Controls (63 Subjects)</th>
<th>Sarcoidosis (83 Subjects)</th>
<th>Statistical difference between groups?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headaches</td>
<td>25%</td>
<td>45%</td>
<td>Yes</td>
</tr>
<tr>
<td>Clumsiness</td>
<td>0%</td>
<td>23%</td>
<td>Yes</td>
</tr>
<tr>
<td>Memory Problems</td>
<td>3%</td>
<td>24%</td>
<td>Yes</td>
</tr>
<tr>
<td>Concentration Problems</td>
<td>5%</td>
<td>29%</td>
<td>Yes</td>
</tr>
<tr>
<td>Numbness</td>
<td>3%</td>
<td>15%</td>
<td>Yes</td>
</tr>
<tr>
<td>History of facial weakness</td>
<td>1 (1.6%)</td>
<td>2 (2.4%)</td>
<td>No</td>
</tr>
</tbody>
</table>

With Dr. Laura Koth, MD, UCSF
Sarcoidosis in the central nervous system (CNS) is typically thought to be protean in its potential clinical manifestations...

- Optic Neuropathy
- Meningitis
- Multiple Cranial Neuropathy
- Myelitis
- Pituitary/Hypothalamic
- Hydrocephalus
- Orbital Mass
- Parenchymal Lesions
- Dural Mass

...to have the potential to strike indiscriminately
CNS SARCOIDOSIS

An inflammatory process that tends to infiltrate and extend locally within a contiguous neuroanatomy and usually involves the leptomeninges

- Focal, infiltrative process that usually involves the meninges
- Optic Neuropathy
- Pituitary/Hypothalamic
- Orbital Mass
- Dural Involvement
- Myelitis
- Multiple Cranial Neuropathies
- Hydrocephalus
- Parenchymal Lesion
Diagnosis: Commonly Applied Criteria

**Definite** – Biopsy confirmation from the nervous system + typical clinical syndrome

**Probable** – MRI or spinal fluid evidence of inflammation plus evidence of sarcoidosis elsewhere in the body by biopsy, Kveim testing or 2 out of 3 of the following: gallium scan, typical chest imaging, elevated ACE

**Possible** – Typical clinical syndrome, no biopsy

(Assuming other diagnostic considerations have been excluded)

Zajicek, et. al, *QJM*, 1999
A Modified Approach Emphasizing Pathology...

**Definite CNS Sarcoidosis** – Biopsy from the nervous system, typical clinical syndrome, exclusion of other causes

**Probable Neurosarcoidosis** – Biopsy from somewhere outside the nervous system consistent with sarcoidosis, typical clinical syndrome and exclusion of other causes

**Possible Neurosarcoidosis** – No pathology, typical clinical syndrome

There are many “steroid responsive,” “non-demyelinating” CNS inflammatory syndromes that are not necessarily “sarcoidosis”
## UCSF CNS Sarcoidosis Experience

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total CNS Sarcoidosis (Biopsy-proven) N=39</th>
<th>Definite (CNS Biopsy) N=18</th>
<th>Presumed (extra-CNS Biopsy) N=21</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at neurological syndrome onset</strong></td>
<td>42 years (SD 10.8), range 21-66 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td></td>
<td></td>
<td>51%</td>
</tr>
<tr>
<td><strong>White</strong></td>
<td></td>
<td></td>
<td>55%</td>
</tr>
<tr>
<td><strong>Black/African-American</strong></td>
<td></td>
<td></td>
<td>42%</td>
</tr>
<tr>
<td><strong>Asian (Indian Subcontinent)</strong></td>
<td></td>
<td></td>
<td>3%</td>
</tr>
<tr>
<td><strong>Hispanic/Latino Ethnicity</strong></td>
<td></td>
<td></td>
<td>10%</td>
</tr>
<tr>
<td><strong>Family history of sarcoidosis</strong></td>
<td></td>
<td></td>
<td>4 (10%)</td>
</tr>
<tr>
<td><strong>Known diagnosis of sarcoidosis in another organ at time of neurological presentation</strong></td>
<td>5 (13%)</td>
<td></td>
<td>(87% did not have known sarcoidosis at first neurological presentation)</td>
</tr>
<tr>
<td><strong>Chest sarcoidosis evident on conventional imaging at initial CNS presentation</strong></td>
<td>58%</td>
<td></td>
<td>(42% did not have “pulmonary” involvement)</td>
</tr>
<tr>
<td><strong>Any extra-CNS sarcoidosis evident clinically or radiologically at initial CNS presentation</strong></td>
<td>65%</td>
<td></td>
<td>(35% did have “isolated” neurosarcoidosis initially*)</td>
</tr>
<tr>
<td><strong>Whole Body PET provided diagnostic insight beyond conventional CT</strong></td>
<td></td>
<td></td>
<td>3/7 (43%)</td>
</tr>
</tbody>
</table>

*But at least half of those with “isolated” disease went on to exhibit subclinical extra-CNS disease over time*
## UCSF CNS Sarcoidosis Experience - 2

<table>
<thead>
<tr>
<th>Test</th>
<th>Biopsy Proven CNS Sarcoidosis N=39</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum ACE Elevated (&gt;67)</td>
<td>15%</td>
</tr>
<tr>
<td>N=32</td>
<td></td>
</tr>
<tr>
<td>CSF ACE elevated</td>
<td>17%</td>
</tr>
<tr>
<td>N=18</td>
<td></td>
</tr>
<tr>
<td>CSF Pleocytosis (&gt;5 WBC)</td>
<td>77%</td>
</tr>
<tr>
<td>N=31</td>
<td></td>
</tr>
<tr>
<td>CSF Protein elevation (&gt;50)</td>
<td>69%</td>
</tr>
<tr>
<td>N=32</td>
<td></td>
</tr>
<tr>
<td>CSF Glucose Abnormally Low</td>
<td>33%</td>
</tr>
<tr>
<td>N=30</td>
<td></td>
</tr>
<tr>
<td>Oligoclonal bands</td>
<td></td>
</tr>
<tr>
<td>Present (4 or more)</td>
<td>31%</td>
</tr>
<tr>
<td>N=26</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>46%</td>
</tr>
<tr>
<td>Matched (bands in serum and CSF)</td>
<td>23%</td>
</tr>
<tr>
<td>N=26</td>
<td></td>
</tr>
<tr>
<td>IgG index elevated</td>
<td>52%</td>
</tr>
<tr>
<td>N=23</td>
<td></td>
</tr>
</tbody>
</table>

WASOG meeting, unpublished, data as of 9/2012
## UCSF Neurosarcoidosis Experience – 3

### Major Neurological Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningitis</td>
<td>20</td>
</tr>
<tr>
<td>Myelopathy (spinal cord syndrome)</td>
<td>11</td>
</tr>
<tr>
<td>Optic Neuropathy</td>
<td>9</td>
</tr>
<tr>
<td>Sellar involvement</td>
<td>9</td>
</tr>
<tr>
<td>Multiple Cranial Neuropathies</td>
<td>4</td>
</tr>
<tr>
<td>Brainstem Syndrome</td>
<td>3</td>
</tr>
</tbody>
</table>

- **Meningitis**: 20 cases
  - 63% required ≥ cane to walk at last known follow-up

- **Myelopathy (spinal cord syndrome)**: 11 cases
  - 63% required ≥ cane to walk at last known follow-up

- **Optic Neuropathy**: 9 cases
  - 33% with severe bilateral vision loss (no light perception)
  - 66% with permanent visual disability in ≥1 eye

- **Sellar involvement**: 9 cases

- **Multiple Cranial Neuropathies**: 4 cases

- **Brainstem Syndrome**: 3 cases

### Immunosuppresant Use

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids alone</td>
<td>9</td>
</tr>
<tr>
<td>Any oral steroid-sparing therapy</td>
<td>24</td>
</tr>
<tr>
<td>Infliximab (TNF-alpha inhibitor)</td>
<td>9</td>
</tr>
</tbody>
</table>

### Clinical Follow-up

<table>
<thead>
<tr>
<th>Follow-up Parameter</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total follow-up from initial presentation</td>
<td>4 years (IQR 2-7 years)</td>
</tr>
<tr>
<td>Last known EDSS</td>
<td>2.75 (IQR 1-6), range 0-8</td>
</tr>
<tr>
<td></td>
<td>38% required ≥ cane to walk (half had myelopathy)</td>
</tr>
</tbody>
</table>

WASOG meeting, unpublished, as of 9/2012
In our analysis focusing on biopsy-proven cases…

-- Neurosarcoidosis tends to be characterized by a characteristic nodular enhancing appearance on MRI

-- The enhancement often extends to and involves nearby meningeal spaces
Nodular enhancing appearance on MRI – 1

Syndrome: Vision Loss (Optic Neuropathy)

CNS Biopsy:
Noncaseating Granulomatous Inflammation
Nodular, infiltrative enhancing appearance on MRI – 2

Syndrome: Spinal Cord
Nodular enhancing appearance on MRI – 2
*(same patient as last slide)*
We are doing research using ultra-high magnetic field MRI (more powerful than currently available in the hospital) to learn more about how to improve non-invasive diagnosis of sarcoidosis.

Hypothesis: We think this dark area is due to iron content in macrophages as part of active granulomatous inflammation.

Presented as a platform at the 2012 American Academy of Neurology Meeting.
Monitoring Disease Activity in CNS Sarcoidosis

- MRI is an important complement to physical examination (as the scans often look worse than the patient and can serve as an “early warning system”)

- CNS sarcoidosis tends to “relapse” by waxing and waning within the same general neuroanatomical distribution or from meningeal involvement

- Be wary of completely new “out of the blue” neurological symptoms
A 10 Year View of Brain Biopsy-Proven CNS Sarcoidosis…

The disease extends and spreads through regional propagation.

- **Nasal Biopsy**
- **Brain Biopsy = sarcoidosis**

**Corticosteroids**

**Addition of Azathioprine**

- **Infliximab**
  - 5 mg/kg load then Q8 weeks
  - 7 mg/kg Q6 weeks

**Blindness**

**Hypopituitarism**

**Cognitive Impairment**

**Cognitive Problems Resolved**

**CSF Exam:**
- 9 WBC
- Glucose 50
- Protein 81
- CSF ACE <3

**CSF Exam:**
- 7 WBC
- Glucose 52
- Protein 112
- IgG Index 0.9
- 4 OCBs
- CSF ACE <3
A 6 Year View of CNS Biopsy-Proven Sarcoidosis...
The disease spreads by regional propagation, waxing and waning over years

CNS biopsy

Baseline  40 months  4 months  22 months  2 years  27 months  28 months  30 months  3 years  40 months

Corticosteroids, taper then increase, then taper...

42 months  4 years  53 months  56 months  59 months  65 months  66 months  69 months  70 months

Stopped methotrexate  Stopped Steroids  Pred 60 mg  Taper  Pred 10 mg  Pulse steroids + azathioprine  Infliximab

Methotrexate trial
A Longitudinal View of CNS Biopsy-Proven CNS Sarcoidosis

It spreads through regional propagation – and can resurge with a vengeance

IV then PO corticosteroids  Steroid Taper  Steroids + MTX  Infliximab

Baseline  + 1 month  + 3 months  + 6 months  + 7 months  + 11 months  + 14 months

Bilateral vision loss, weight loss, fatigue, hyponatremia  Back to Normal  Vision worsens, hyponatremia again  Substantial but incomplete visual recovery (severe constricted fields)

Baseline  + 1 month  + 3 months  + 6 months  + 7 months  + 11 months  + 14 months

Optic Nerve Sheath Biopsy

CSF:
- 67 WBC
- Glucose 44 (serum 99)
- Protein 89

IV Contrast not given for this study
Treatment of CNS Sarcoidosis

- The general rule is to treat involvement in each organ system as its own problem, rather than just treating “sarcoidosis”

- When the central nervous system is involved and symptomatic, we almost always offer treatment

- When the peripheral nervous system is involved – and clearly caused by sarcoidosis as opposed to another problem, we also usually offer treatment
Evolving algorithm for treatment of CNS Sarcoidosis

1) Corticosteroids – start high and taper slowly (if able)

1) Methotrexate –or– Azathioprine–or–Mycophenolate *

3) Infliximab-- (Second-line agent in high-risk patients?)

*Some experts prefer leflunomide or other oral steroid-sparing agents at this tier
Neurological symptoms in people with sarcoidosis could...

1) Have nothing at all to due with sarcoidosis

2) Be caused directly by the granulomatous inflammatory process of sarcoidosis ("Neurosarcoidosis")

3) Be a consequence of having sarcoidosis, but not due to active granulomatous inflammation at the site of tissue injury (Neurological symptoms secondary to having sarcoidosis, but not "neurosarcoidosis")

4) Be a complication of therapy or the immunological alterations of sarcoidosis (infection, medication side effect, other complication)
Meningitis in a patient with established pulmonary sarcoidosis

- 44 year-old man with histologically confirmed pulmonary sarcoidosis (stage 2 initially), treated with corticosteroids and then, due to worsening symptoms when tapering, to oral methotrexate.

- Three years into the disease, he develops subacute headache, double vision (6th nerve palsy), imbalance and urinary retention
MRI Brain — “Linear and nodular leptomeningeal enhancement... These findings are likely related to an inflammatory or infectious process including sarcoid, but other infectious etiologies are not excluded. Recommend correlation with a spinal fluid exam”

MRI Spine  “Multiple focal enhancing lesions throughout the entire spinal cord are compatible with neurosarcoidosis.”

CSF Exam  Inflammation
Follow-up

• On close exam, there was a scalp rash that evolved under the hair (“Shingles”)

• Spinal fluid VZV PCR (a test for the chicken pox/varicella virus in the spinal fluid) was highly positive

**Diagnosis:** Meningitis from Varicella Zoster Virus (Chicken-pox virus reactivation) in an immunosuppressed patient with pulmonary sarcoidosis – an unfortunate infectious complication of treatment
Conclusions

• Neurosarcoidosis is an important and sometimes aggressive manifestation of sarcoidosis that affects a minority of people with the disease – expert consultation is recommended to guide diagnosis and treatment

• Some neurological symptoms are very common in people with sarcoidosis, such as fatigue, headaches, tingling and mild concentration problems, but are not “neurosarcoidosis”

• Treatment of neurosarcoidosis should be guided by the neurological syndrome – early initiation of therapy is probably indicated for severe or high risk cases