Neurosarcoidosis occurs in 5-15% of patients with Sarcoidosis. This diagnosis of exclusion may be challenging due to the presentation of various symptoms and clinical manifestations requiring coordination of full scope ocular and medical care.

I. **Case History**
   a. Patient Demographics: 57 year old, black, male
   b. Chief Complaint: presented for f/u for a repeat HVF and IOP check. He complained of having had a "funny feeling" (like a seizure) about a month ago - but it wasn't a "full seizure".
   c. Ocular History: glaucoma suspect, h/o anterior uveitis, cataracts
   d. Medical History: Pulmonary sarcoidosis, Seizures, Chronic sinusitis, Osteoporosis, Iron deficiency anemia, Hypertension, Depression
   e. Medications: Alendronate 5mg, Carbamazepine 200mg, Mirtazapine 30mg
   f. Ocular Medications: Alphagan BID OU
   g. Allergies: NKDA
   a. Family Ocular History: none

II. **Pertinent Findings**
   a. Vision (cc): 20/20-1 OD; 20/20-2 OS; 20/20 OU
   b. Pupils: ERRL (–)APD OU
   c. T\textsubscript{A} IOP: 11mmHg OD, 12mmHg OS @ 11:34am
   d. SLE: Nasal and Temporal pingeuclea OU, 1+-2 Nuclear Sclerosis OU, all else normal
   e. Undilated DFE: 0.6 thinner with possible inf notch OD, 0.6 thinner inf but sloping superiorly OS, no hemes OU, pink/distinct ou
   f. HVF at this visit: early superior temporal defect respecting vertical midline OD, mod sup nasal defect respective vertical midline OS. Both fields have excellent reliability.
   g. GDx: inferior thinning, NFI = 27 OD, superior thinning, NFI 39 OS.
      i. Although the superior field defects OU matched the OCT from previous visit (showed inferior thinning OS>OD) and the GDx (showed inferior thinning in OD only), the sup defect in each eye appears to respect the vertical meridian, and thus it appears as a superior right homonymous defect.
   h. Further Glaucoma Testing Results
      i. Last OCT (done at the previous visit 3 months prior):
         1. OD: early inferior thinning
         2. OS: mild to mod inferior thinning
      ii. IOP at this visit: 11mmHg OD, 12mmHg OS
      iii. Pre-tx IOP: 15mmHg OD, 18mmHg OS
      iv. Goal IOP: 10mmHg OD, 12 mmHg OS
      v. Last DFE: 6 months ago
      vi. Last Gonio 2009: 4+ open, (-) pigment OU
      vii. Pachymetry: 549,555,559 OD; 556,556,556 OS
      viii. HVF done at last visit 3 months prior: early superior arc/superior-temporal defect with a few focal spots inferior-nasal, excellent reliability OD, mod superior-nasal defect, excellent reliability OS
         1. Result: superior right homonymous defect.
ix. HVF done 6 months prior: inferior>superior defect (not respecting vertical) OD and superior>inferior defect (not respecting vertical)
   1. This field appears glaucomatous

III. Differential Diagnosis Based on Current Findings and HVF Results
   a. Tumor in the temporal lobe – need MRI or CT imaging to confirm. Temporal lobe lesions can cause a “pie in the sky” visual field defect.
   b. Glaucoma – see rNFL thinning on OCT and GDx. Usually see arcuate scotomas, paracentral defects, nasal step defects and peripheral constriction.
   c. Epilepsy - Repeated seizures and epilepsy can cause lack of oxygen to the brain resulting in a visual field defect
   d. Multiple Sclerosis – inflammatory condition that causes demyelination in the white matter of the brain or spine. MRI is usually diagnostic.
   e. Stroke – ischemic or hemorrhagic event that can occur in any part of the brain. The more posterior the stroke, the more congruous the visual field defect is. Can be detected using MRI.
   f. Infection – can be bacterial, viral, fungal, aseptic, or parasitic.
      i. Encephalitis – swelling or inflammation of the brain. Can be viral, bacterial or due to an infectious condition.
      ii. Meningitis – inflammation of the membranes around the brain and spinal cord. Associated with headache and neck stiffness and can be life threatening. Need CBC and LP for CSF analysis.
   g. Combination

IV. Further Review of Patient’s Ocular History
   a. Went as far back as 8 years prior when patient first had a VF done
      i. Result: HVF respected the midline OU
   b. VFs from 2003 onwards have remained stable
      i. Showed a superior nasal defect OD and a superior temporal defect with inferior focal defects OS
      ii. VF defects RESPECTED THE MIDLINE in both eyes

V. Laboratory/Imaging Findings
   a. Chest X-ray/CT
      i. 10 years ago: Findings are consistent with sarcoidosis with hilar lymphadenopathy and parenchymal lung disease.
      ii. This year: Continued sequelae of sarcoidosis with the lung parenchymal abnormalities appearing stable to maybe have slightly progressed
   b. MRI of Brain and Orbits
      i. 2009: decreased abnormal signal of the mesial left temporal lobe without enhancement, consistent with leptomeningeal neurosarcoidosis. Within the periventricular white matter, multiple focal areas of increased T2 and flair signal.
      ii. 2006: Unchanged mild edema and enhancement in the mesial left temporal lobes, consistent with leptomeningeal neurosarcoidosis.
      iii. 2004: demonstrates mild periventricular white matter disease and mild enhancement adjacent to the mesial left temporal lobe. Leptomeningeal involvement from neurosarcoid. Stable from 2003
      iv. 2003: a focal or enhancement in the left temporal lobe which demonstrates hyperintensity on flair imaging. This is suspicious for neurosarcoidosis involvement.
c. Lab Findings
   i. Serum ACE Level: 45, high normal (Norm: 9-67U/L)
   ii. CBC: normal
   iii. HIV 1 & 2 Antibody: nonreactive
   iv. ANA: negative
   v. RF: negative
   vi. IgG index: 1654 - High (range 652-1375)
   vii. ESR: 18 (normal) at last lab test. Has been elevated in previous lab results secondary to sarcoidosis inflammatory flare ups.

VI. Final Diagnosis – Neurosarcoïdosis
   a. Treatment (Consistent with MRI findings)
      i. May 2003: Pt started on 20mg oral prednisone daily and discontinued April 2004
      ii. November 2004: Pt restarted on 40mg oral prednisone daily
      iii. Pt slowly tapered 5mg oral prednisone every other day over the course of a little under 5 years
      iv. Discontinue prednisone October 2009

VII. Sarcoidosis
   a. Epidemiology\textsuperscript{1-3}
      i. Non-caseating, granulomatous inflammatory disease of unknown etiology
      ii. Can affect multiple organs
      iii. Higher occurrence rate seen in Northern Europeans and African Americans
      iv. Prevalence is 20-40:100,000
      v. Females affected more than Males
      vi. More common in 3\textsuperscript{rd} to 4\textsuperscript{th} decade of life
      vii. Mortality rate is ~1-5%
   b. Description/Etiology\textsuperscript{1,4,5,6}
      i. Microbial Agents
         1. Studies have shown *Mycobacteria tuberculosis* and *Propionobacterium acnes*, and *Borelia* to be associated with sarcoidosis
      ii. Environmental/Occupational Agents
         1. Include rural living, fireplaces, wood stoves, home mold exposure, pesticides, fire rescue workers
         2. Exposure to inorganic agents: beryllium, nickel, chromium, aluminum, synthetic mineral fibers and zirconium
      iii. Genetics
         1. Association with the HLA phenotypes have been reported in some studies
      iv. Although the ACCESS study (A Case Control Etiologic Study of Sarcoidosis) and other follow up studies have supported these etiologies, they are still not proven
   c. Systemic Involvement\textsuperscript{3-5}
      i. Pulmonary - the lungs are affected 90% of the time
      ii. Lymph nodes
      iii. Eyes
iv. Skin - Erythema nodosum, lupus pernio, maculopapular lesions, subcutaneous nodules
v. Liver
vi. Endocrine glands
vii. Musculoskeletal
viii. Kidneys
ix. Spleen
d. Ocular Manifestations\textsuperscript{3,4}
i. Occur in approximately 30-60% of patients
ii. More common in women (68%)
   1. Anterior uveitis
      a. most frequent ocular manifestation of sarcoidosis - Can be seen early in up to 91% of patients
      b. Bilateral granulomatous uveitis is the most common finding
      c. Mutton-fat KP’s on the inferior cornea
      d. Keoppe and busacca nodules
   2. Granulomas or nodules in the TM &/or PAS
   3. Posterior uveitis
   4. Vitreous snowballs or “string of pearls”
   5. Periphlebitis (candlewax drippings)
   6. Multiple peripheral chorioretinal lesions
   7. Peripheral neovascularization can occur
   8. Orbital sarcoid
      a. Tumor or infiltration of the lacrimal gland
   9. Optic nerve
      a. Papilledema, optic neuropathy, disc elevation, atrophy, optic disc granulomas
  10. Post chiasmal
      a. Compression, infiltration, vascular changes
  11. Ocular motor dysfunction
      a. Cranial nerve palsies
  12. Pupillary dysfunction
      a. Horner’s syndrome, tonic pupils, argyll robertson pupils, uveitis

iii. Chronic ocular symptoms can lead to the development of cataracts, glaucoma and CME

VIII. Neurosarcoidosis
a. Description/Epidemiology\textsuperscript{5,7}
i. Occurs in ~ 5-15% of pt’s with sarcoidosis
ii. Majority of patients with NS have sarcoidosis in other organs
iii. Axonal damage is the most common consequence of inflammation, not demyelination
iv. The basal meninges are most commonly involved
b. Neurological Manifestations\textsuperscript{5,7,8,9}
i. Cranial neuropathy (~50-75%)
   1. Most common manifestation
   2. CN 7 is the most commonly involved nerve
3. Can be unilateral or bilateral
   ii. Parenchymal involvement (~10-15%)
       1. Hypothalamic dysfunction is most common
   iii. Encephalopathy and vasculopathy
       1. Commonly occur together
       2. TIA's and ischemic stroke-like events can occur
   iv. Seizures (~5-20%)
       1. Can be generalized or focal
   v. Meningeal involvement
       1. Include aseptic meningitis, mass lesions and hydrocephalus
   vi. Myelopathy
       1. Clinical presentation can vary depending on the location and extent
          of disease in the spinal cord
   vii. Peripheral neuropathy (~15-18%)
       1. Usually mild and asymptomatic, however, the course can be acute,
          chronic or relapsing
       2. Can be focal or multifocal, affecting all levels of nerve fibers

c. Study Of Neurosarcoidosis and Seizures
   i. Sponsler et al. did a literature review of neurosarcoidosis and seizures
   ii. Results showed:
       1. Mortality was increased by 20% when seizures were associated with
          NS
       2. 47% of the 30 pts with NS and seizures died ranging from 1 month
          to 10 years after the onset of CNS symptoms
       3. Type of seizure affected the survival rate
       4. Timing of the seizure did not affect the outcome for survival

d. Imitators of Neurosarcoidosis
   i. Multiple sclerosis
   ii. Lymphoma
   iii. Craniopharyngioma
   iv. Primary CNS neoplasia
   v. CNS infections
      1. neurosyphilis, HIV, toxoplasmosis

e. Zajicek Criteria for Diagnosis NS
   i. Definite
      1. Clinical presentation of NS
      2. Presence of positive nervous system histology
      3. Exclusion of other diagnoses
   ii. Probable
      1. Clinical syndrome suggesting NS
      2. Lab support for CNS inflammation
      3. Evidence of systemic sarcoidosis
      4. Exclusion of other diagnoses
   iii. Possible
      1. Clinical presentation suggestive of NS
      2. Exclusion of other diagnosis
      3. The above criteria are not met

f. Diagnostic Testing
i. Kveim Test2,3,5
   1. Subcutaneous injection of sarcoid tissue from human spleen, liver or lymph nodes
   2. If positive, a biopsy will show noncaseating granulomas 4-6 weeks after the injection
   3. Limited test due to the difficulty of obtaining the materials
   4. Sensitivity and specificity are not higher than other tests

ii. Serum ACE Levels2,3,5,6,9
   1. Significantly elevated in patients with active sarcoidosis
   2. Non-specific as it can be elevated in other conditions
   3. Due to an increased release of ACE from macrophage derived epitheloid cells
   4. Not very sensitive

iii. Gallium Scans2,3,5,9,10
   1. Poor specificity
   2. Scan alone may help in diagnosing new onset ocular sarcoidosis but is not sensitive in detecting CNS involvement
   3. Combining the serum ACE level with the gallium scan can produce a higher sensitivity and specificity in diagnosing sarcoidosis

iv. Lysozyme Levels6,9
   1. Serum lysozyme levels have shown to be a more sensitive test of sarcoidosis activity
   2. Less specific than serum ACE levels
   3. Diagnostically limited

v. Chest X-ray3,4
   1. Simple and less expensive diagnostic test
   2. Bilateral hilar lymphadenopathy
      a. Stage 1: without lung involvement
      b. Stage 2: with parenchymal involvement
      c. Stage 3: lymphadenopathy may resolve, parenchymal involvement only
      d. Stage 4: end stage lung involvement → pulmonary fibrosis

vi. MRI2,3,5-7,9
   1. Abnormalities can be seen in up to ~80% of patients
   2. With gadolinium contrast - preferred imaging choice to evaluate for NS
   3. Helpful in finding and localizing site of lesion
   4. Lesions in the periventricular matter are hypersensitive on T-2 weighted scans
   5. Leptomeningeal involvement is the most common imaging abnormality (~40%)
      a. Predilection for the basilar meninges
   6. Optic nerve is more commonly involved radiographically
   7. Highly sensitive but not specific in diagnosis NS

vii. Bronchoalveolar Lavage Fluid6,3
   1. Helpful in diagnosing and follow up for pulmonary sarcoidosis
   2. Findings consistent with sarcoidosis:
a. Increases total cell count, primarily lymphocytes
b. Nearly normal eosinophils and PMNs
c. Absence of plasma cells

viii. PET Scan\textsuperscript{6,7}
1. Nonspecific measurement of tissue metabolic activity
2. Useful in identifying alternative biopsy sites
3. Can possibly determine the extent of organ involvement

ix. VEP\textsuperscript{5,6}
1. Visual and brainstem auditory responses are usually abnormal even in pt’s without ocular or neurological symptoms
2. May be able to help with early diagnosis of neuro-ophthalmic sarcoidosis
3. Can be useful for monitoring
4. Not specific

x. CSF Examination\textsuperscript{5,7,10}
1. Up to 80% of patients with NS will show some CSF abnormalities (include increased protein and lymphocytes)
2. Elevated IgG index can occur
3. CD4:CD8 ratio of lymphocytes can be elevated in CSF in NS
4. CSF ACE is elevated in \sim 50\% of NS patients
5. nonsensitive and nonspecific

g. Treatment of Neurosarcoidosis
i. Corticosteroids\textsuperscript{3,5,6,9}
1. Mainstay of initial therapy for NS
2. Usually started in high doses and gradually tapered
3. 40-80mg of prednisone for 4-8wks
4. Many patients require alternative Tx due to failure/intolerable systemic side effects with steroids
5. Side Effects: glucose intolerance, osteoporosis, obesity, cataracts

ii. Alternative Immunosuppressive Agents
1. Methotrexate\textsuperscript{3,5,11}
   a. Antimetabolite with antinflammatory and immunosuppressive factors
   b. Well tolerated
   c. Main Side Effect: liver toxicity, interstitial pneumonitis
   d. Folinic acid can reduce drug toxicity
2. Cyclophosphamide\textsuperscript{3}
   a. Alkylating agent
   b. Lowers the function and number of lymphocytes
   c. Usually takes several months to show a response
   d. Side Effects: higher risk for infections, infertility, malignancy
3. Cyclosporine\textsuperscript{3,5,9}
   a. Effective in NS, ineffective in pulmonary sarcoidosis
   b. Inhibits T cells
   c. Best when used as an adjunct with steroids
   d. Main Side Effect: hypertension and renal dysfunction
4. Azathioprine\textsuperscript{3,5}
a. Major advantage: Moderate cost and tolerability  
b. Monitor blood counts and liver function tests  
c. Most common Side Effect: gastrointestinal problems  

5. Chlorambucil\textsuperscript{3,5}  
   a. Most common Side Effect: bone marrow suppression  

6. Chloroquine/Hydroxychloroquine\textsuperscript{3}  
   a. Major Side Effect: renal toxicity  
   b. Need regular eye exams to monitor for toxic effects  

7. Radiation Therapy\textsuperscript{5,7}  
   a. Usually considered as a last resort when all other treatment fails  
   b. Recommended dose is 19.5Gy  
   c. Simultaneous use of corticosteroids or immunosuppressive agents is usually required  

iii. Study on NS Therapy\textsuperscript{12}  
   1. 78 patients but only 48 fit the criteria by Zajicek  
   2. 20 pts were given pulse &/or maintenance corticosteroids, 26 were given immunosuppressive & steroid tx and 2 received no tx  
   3. With steroids alone: 35% improved, 55% remained stable and 10% got worse  
   4. With alternative tx & corticosteroids: 69% improved, 15% remained stable, 15% got worse  

IX. Prognosis of Neurosarcoïdosis\textsuperscript{8,9,13}  
   a. While the majority of patients respond well to treatment, approximately 1/3 of patients will relapse  
   b. Cranial neuropathies have better prognosis  
   c. Intracranial NS including cerebral, mass or spinal lesions, seizures and hydrocephalus are more likely to relapse and have a poorer prognosis  

X. Recap/Patient’s Current Status  
   a. Based on the Zajicek criteria for diagnosing, this patient is “Probable” for neurosarcoïdosis  
      i. No record of positive histological biopsy of the nervous system, therefore not definite  
      ii. Does have evidence of systemic sarcoïdosis (Chest x-ray)  
      iii. Does have lab support for CNS inflammation (MRI evidence)  
      iv. Does have clinical syndrome suggesting NS (seizures)  
   b. Pt is not currently taking any medications for systemic sarcoidosis  
   c. HVF stable, however, pt likely has combination of neurosarcoïdosis and glaucoma. Pt will continue treatment with Alphagan.  
   d. Another MRI is scheduled for October 2011  

XI. Conclusion  
   a. Sarcoïdosis is a multi-organ disease which can also affect any part of the eye and visual system.  
   b. While the neurological aspect is rare, it should always be considered as a differential especially since it is a diagnosis of exclusion.  
   c. It is important to perform the correct testing for a definitive diagnosis.
d. Treatment should be started according to the clinical presentation to prevent further progression and complications of the disease, systemically and neurologically.

XII. References
11. Lower EE, Broderick JP, Brott TG, Baughman RP. Diagnosis and Management of Neurological Sarcoidosis. Archives of Internal Medicine. 1997 Sep 8;157(16):1864-8