Neurosarcoidosis

Barney J. Stern, MD
University of Maryland
Baltimore, MD

Overview

- Neurological complications of sarcoidosis occur in approximately 5 – 14% of patients with sarcoidosis.
  - Patients with known systemic sarcoidosis can develop neurological symptoms and signs.
  - Patients without known sarcoidosis can develop neurological findings consistent with neurosarcoidosis.
- 50% of neurosarcoidosis patients present with neurological disease at the time of their sarcoidosis diagnosis.

Clinical Manifestations

- Cranial neuropathies
- Meningeal disease
  - Aseptic meningitis
  - Mass lesion
- Hydrocephalus
- Parenchymal disease
  - Endocrinopathy
  - Mass lesion(s)
  - Encephalopathy / micro-vasculopathy
  - Seizures
  - Stroke
- Vegetative dysfunction
- Extra- or intra-medullary spinal canal disease
- Cauda equina syndrome
- Neuropathy
  - Mononeuropathies
  - Axonal or demyelinating
  - Sensory, motor, sensorimotor
- Myopathy
  - Polymyositis
  - Nodule(s)
  - Atrophy

Headache

- Meningeal inflammation
- CNS mass
- Hydrocephalus
- Trigeminal neuropathy
  - Impaired facial / head pain and temperature perception
  - Hyperesthesia and dysesthesia

Stroke Mechanisms

- Ischemic stroke
  - Sarcoidosis is prothrombotic disorder
  - Small or large artery *in situ* thrombosis
  - Cardiogenic emboli
    - Cardiomyopathy
    - Arrhythmia
  - Large artery compression from a granulomatous mass
  - Artery to artery emboli
- Sinovenous thrombosis
- Intracerebral hemorrhage

Ajayi and Stern, 2006

Diagnostic Certainty

- Possible
  - Clinical syndrome and diagnostic evaluation suggest NS. Infection and malignancy are not excluded *or* there is no pathologic confirmation of systemic sarcoidosis
- Probable
  - Clinical syndrome and diagnostic evaluation suggest NS. Alternate diagnoses are excluded. Pathologic confirmation of systemic sarcoidosis.

Diagnostic Certainty

- Definite
  - Clinical presentation suggestive of NS, other diagnoses are excluded, and there is supportive nervous system pathology, *or*
  - The criteria for “probable” NS are met and the patient has had a beneficial response to immunotherapy over a 6 month observation period.

Adapted from Zajicek et al. 1999

Diagnosis of Sarcoidosis

- No known sarcoidosis
  - *Defer treatment so as not to mask systemic disease*
  - *Exclude infection and malignancy*
- Lung, lymph node, ocular disease
- Impaired smell or taste … nasal or olfactory disease
- Dry eyes or mouth … lacrimal, parotid, or salivary gland inflammation

Diagnosis of Systemic Sarcoidosis

- Elevated serum ACE activity
- Hypercalcemia
- Hypercalciuria
- Elevated immunoglobulins
- Anergy
- Chest X-ray
- Thoracic CT

- PFT's including D_{CO}
- Ophthalmologic exam
  - Retinal vasculitis
- **Endoscopic nasal exam**
- Whole-body gallium scan
- **Muscle MRI**
- **Whole-body FDG PET scan**

Known Sarcoidosis … New CNS Mass

- Exclude infection and malignancy
  - Empiric corticosteroid trial
- Poor response to therapy … biopsy mass

CNS Sarcoidosis – Issues Often Forgotten

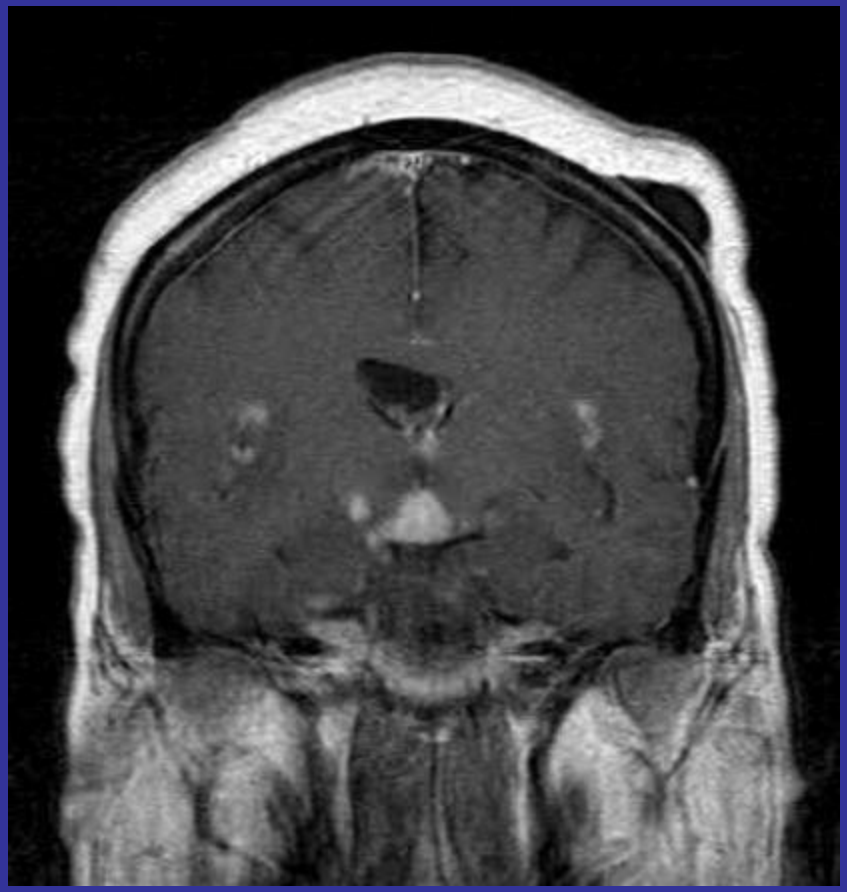
- Libido, menses, galactorrhea, or erectile dysfunction
- Excessive thirst
  - “Osmostat”, diabetes insipidus, hyperglycemia, hypercalcemia (hypercalciuria)
- Altered body temperature, sleep, or appetite
- TFT’s (*hypothalamic hypothyroidism*), prolactin, testosterone or estradiol, FSH, LH, and cortisol

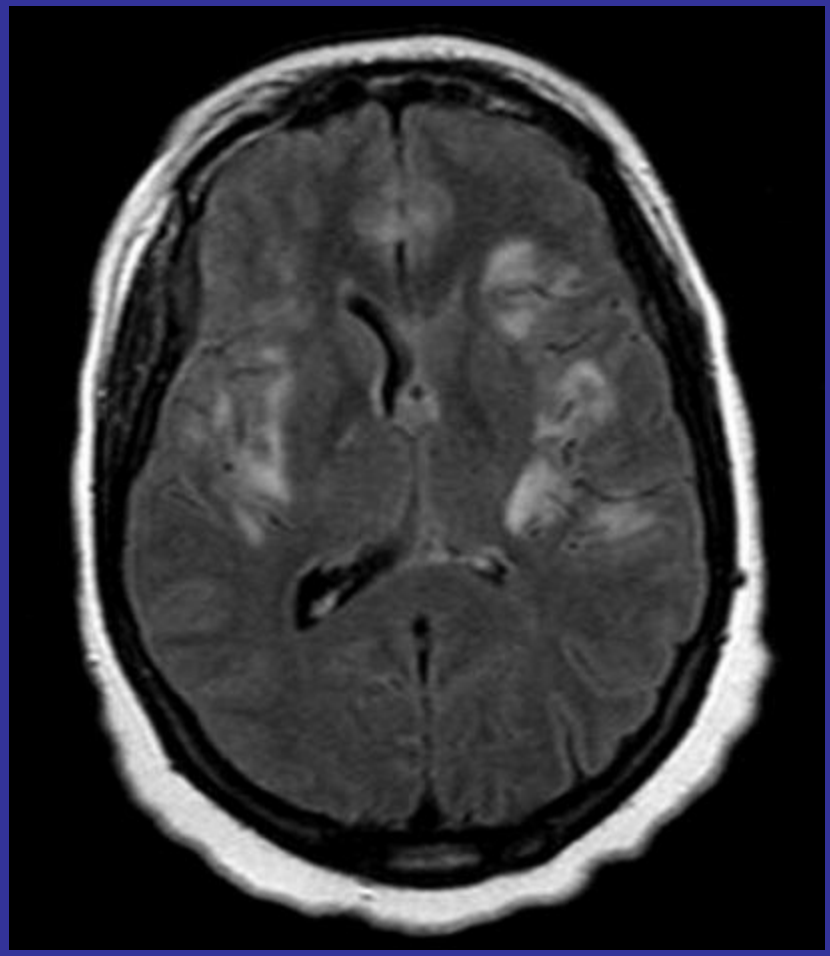
Differential Diagnoses

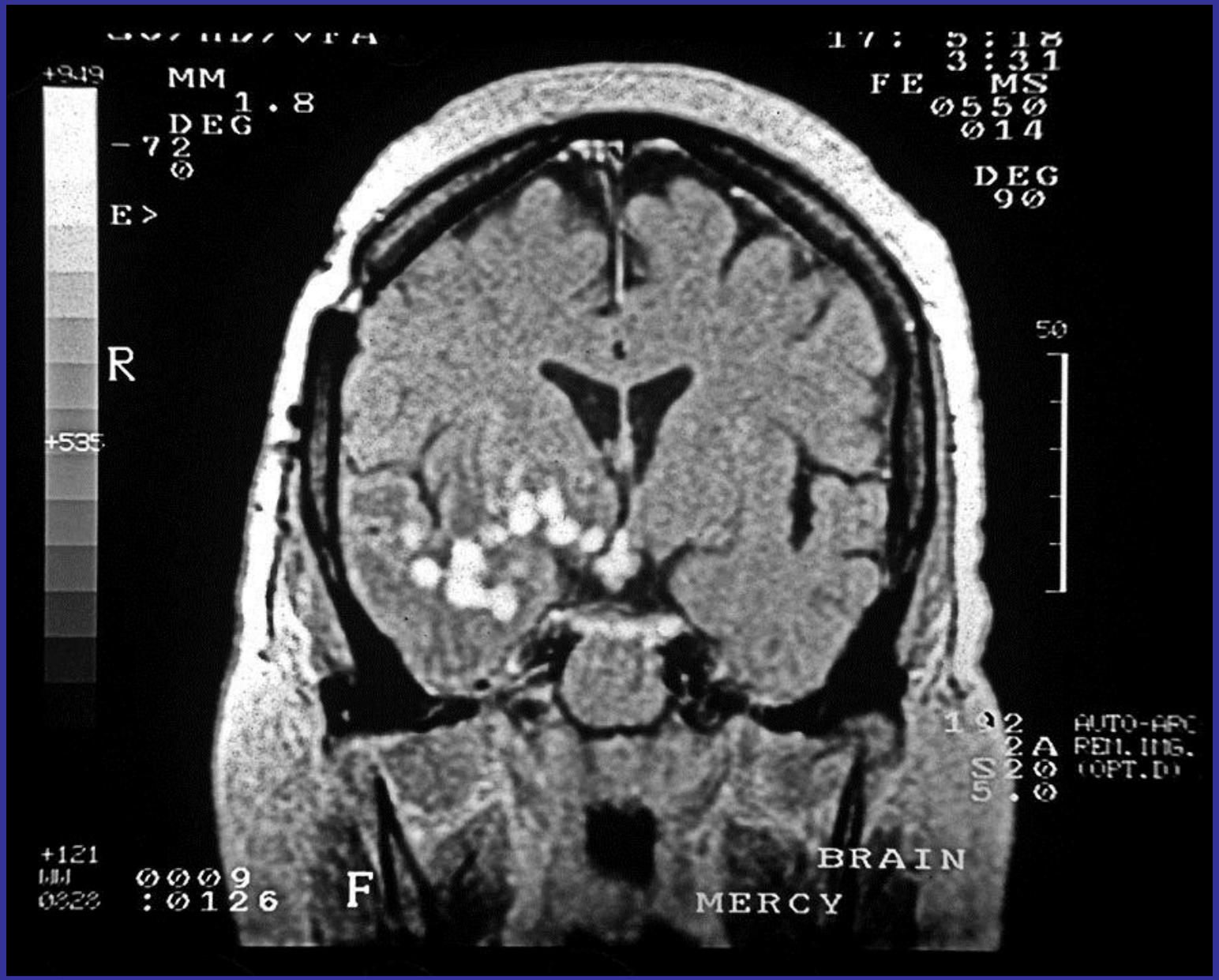
- Low CSF pressure / volume meningeal enhancement
- MS
- Neuromyelitis optica
- Sjögren syndrome
- SLE
- Neurosyphilis
- Neuroborreliosis
- HIV infection
- Lymphoma
- Behçet's disease
- Brucellosis
- Whipple's disease
- Germ cell tumors
- Craniopharyngioma
- Isolated CNS angiitis
- Primary CNS neoplasia
- Lymphocytic hypophysitis
- Pachymeningitis
- Rosai-Dorfman disease
- CMV meningoencephalitis
- Vogt-Koyanagi-Harada
- Toxoplasmosis

Neurodiagnostic Investigations

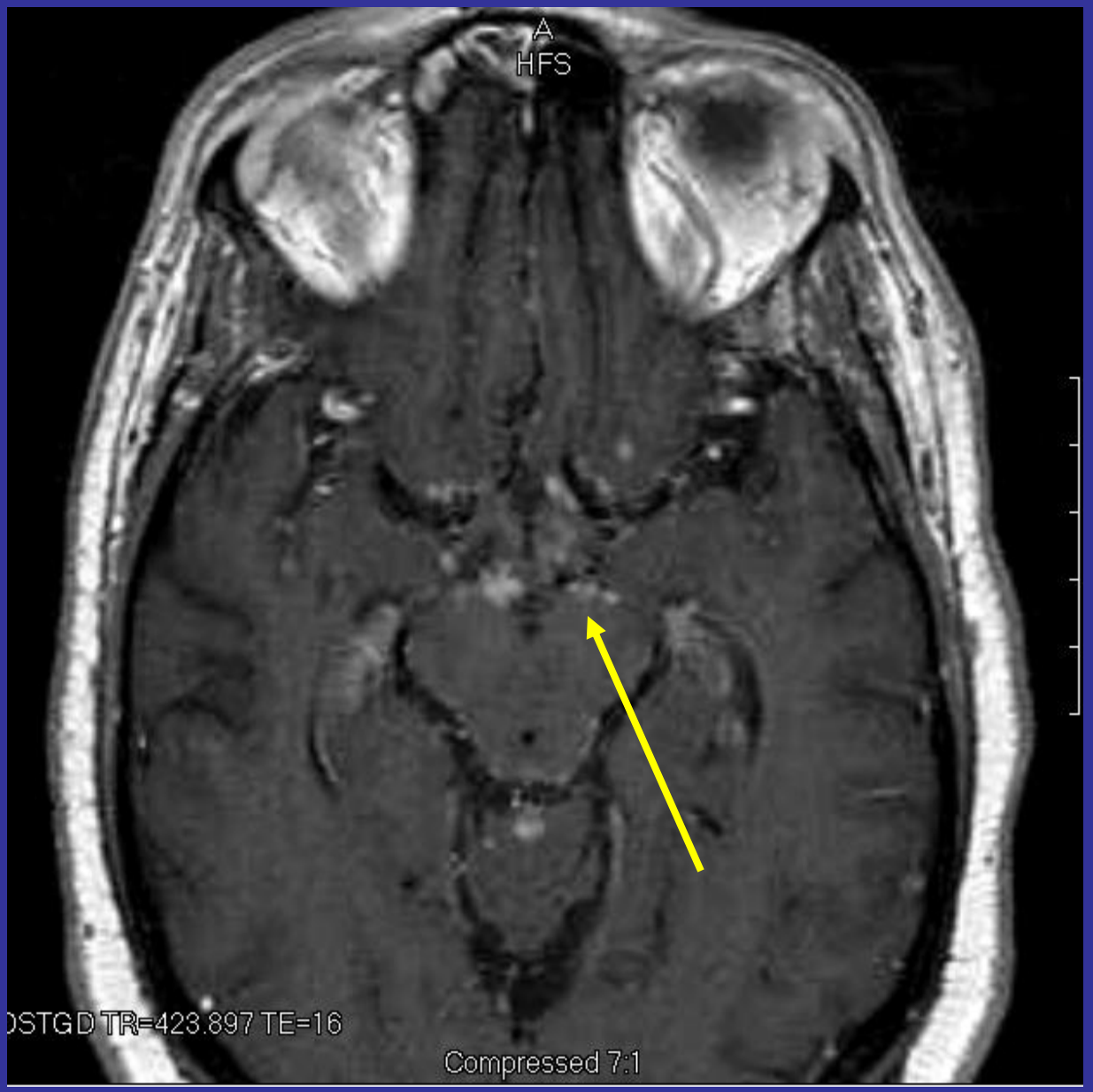
- Brain and spine MRI -/+ contrast
- FDG PET
  - Brain hyper- or hypo-metabolism
- CSF
  - ↑ protein, ↓ glucose, mononuclear pleocytosis
  - ↑ IgG index, + OCB
  - ACE

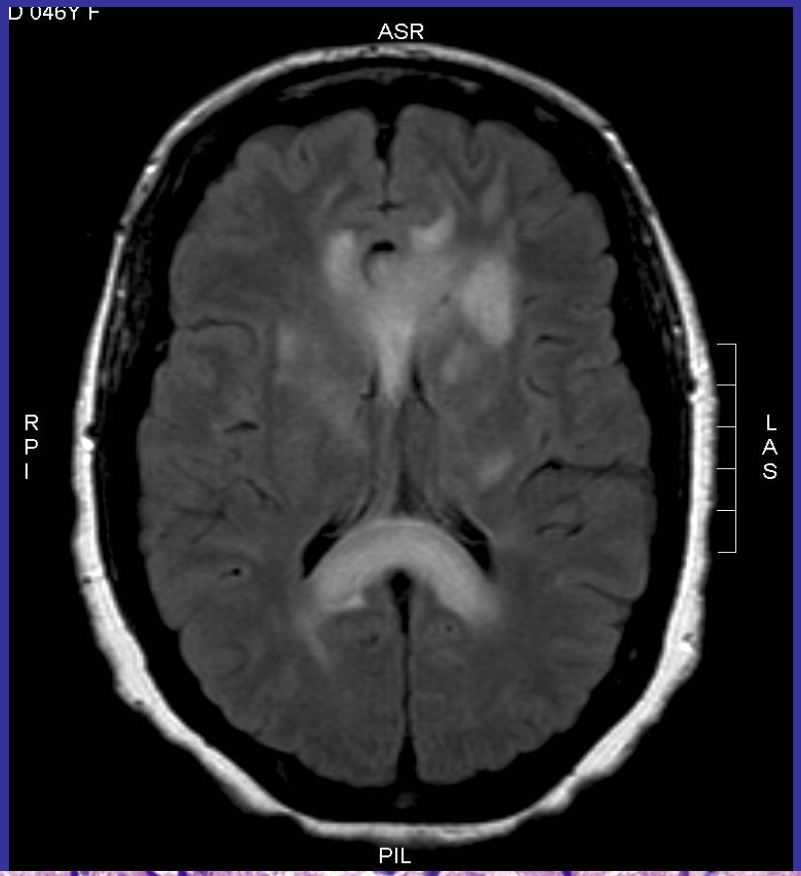


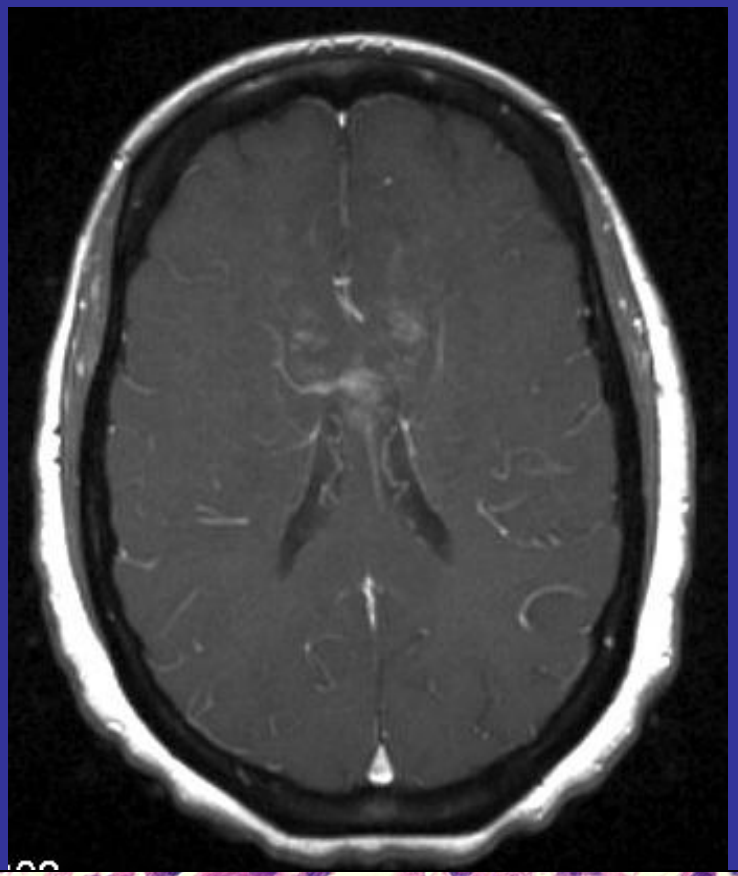


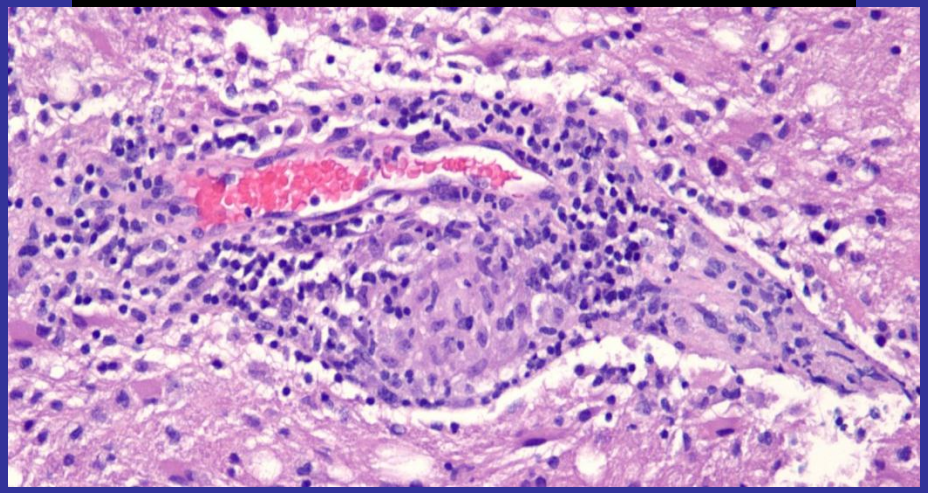


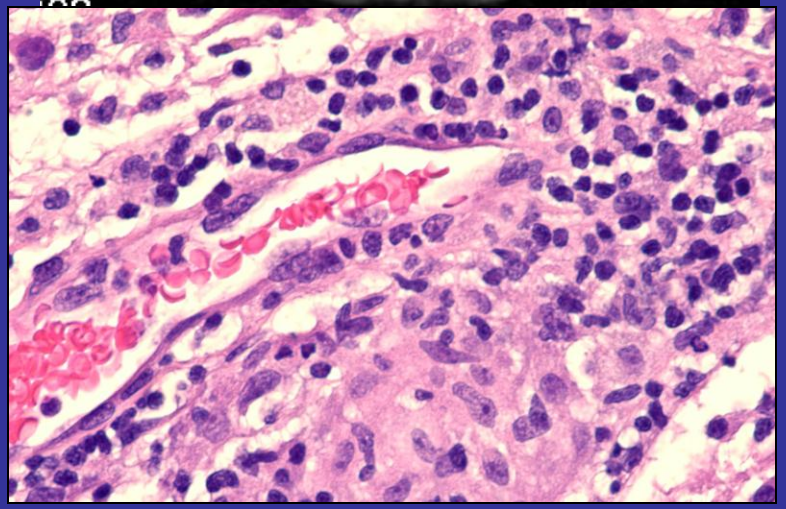
Courtesy of Dr. J. Corbett

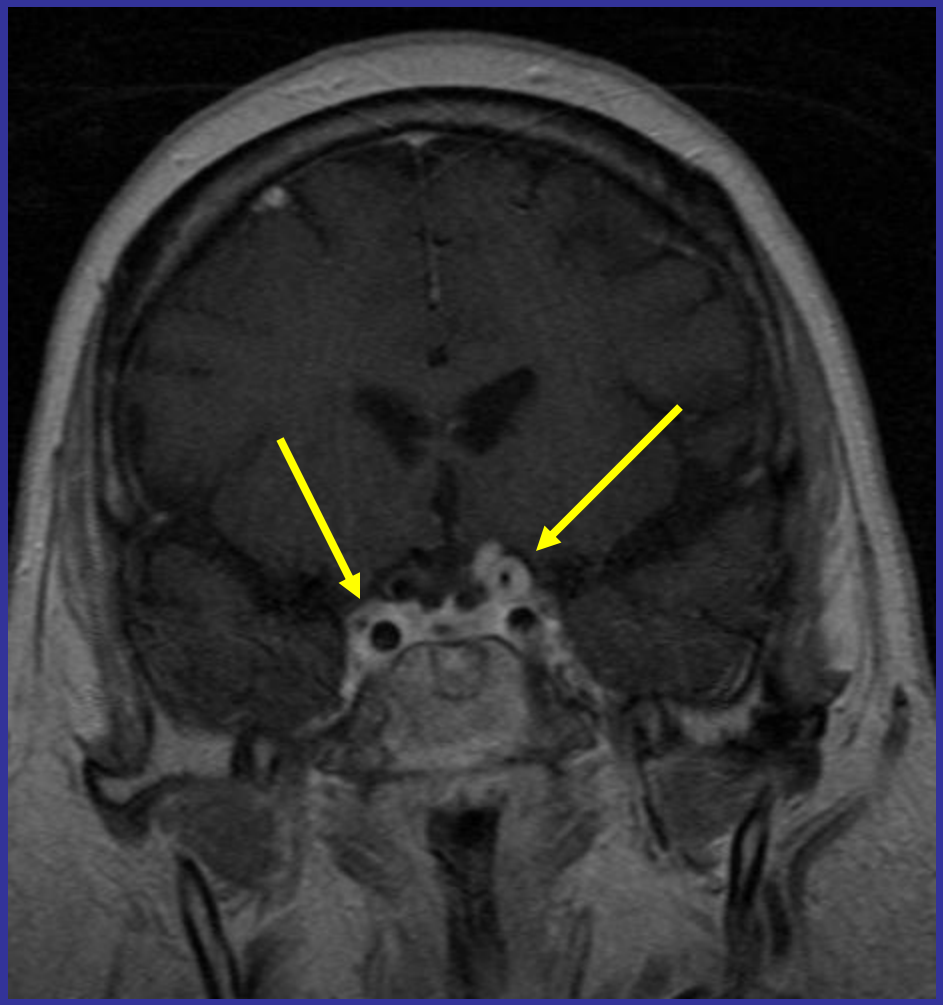

A
HFS
STGD TR=423.897 TE=16
Compressed 7:1

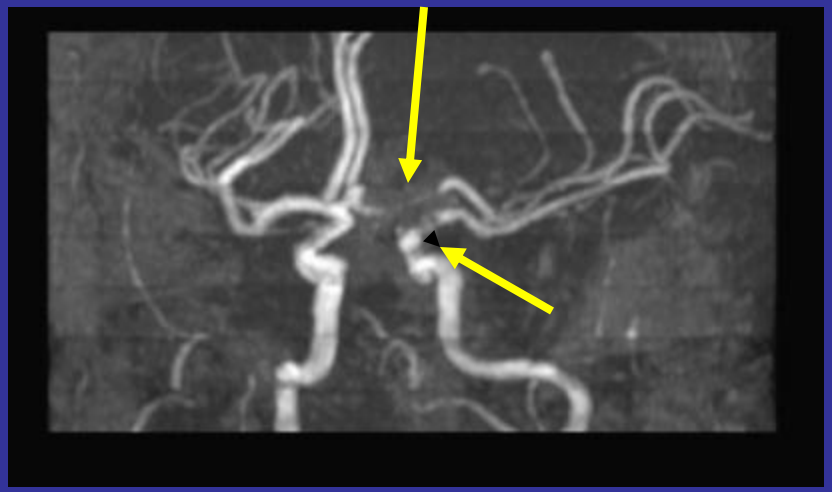

ASR
R
P
I
L
A
S
PIL

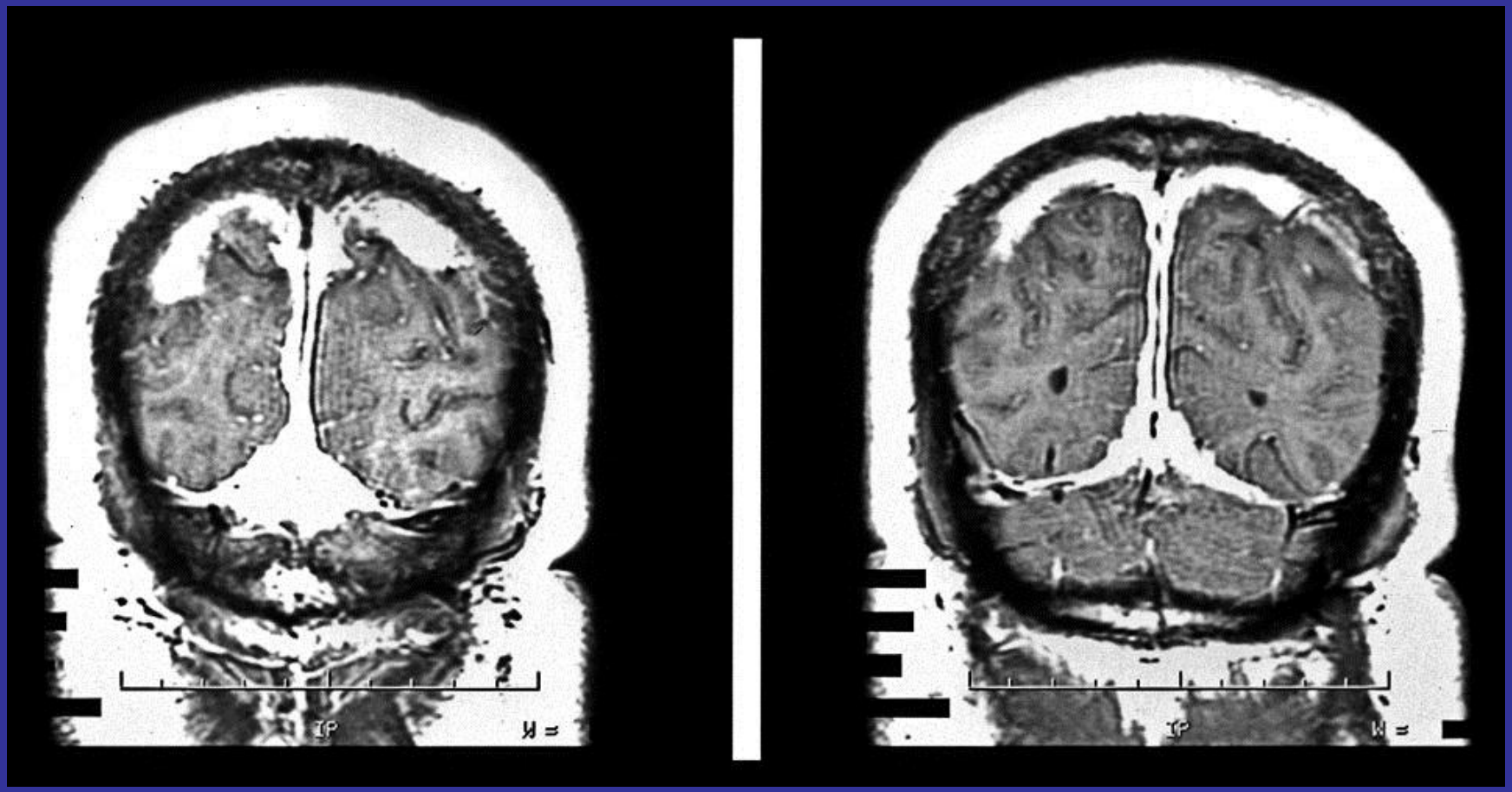




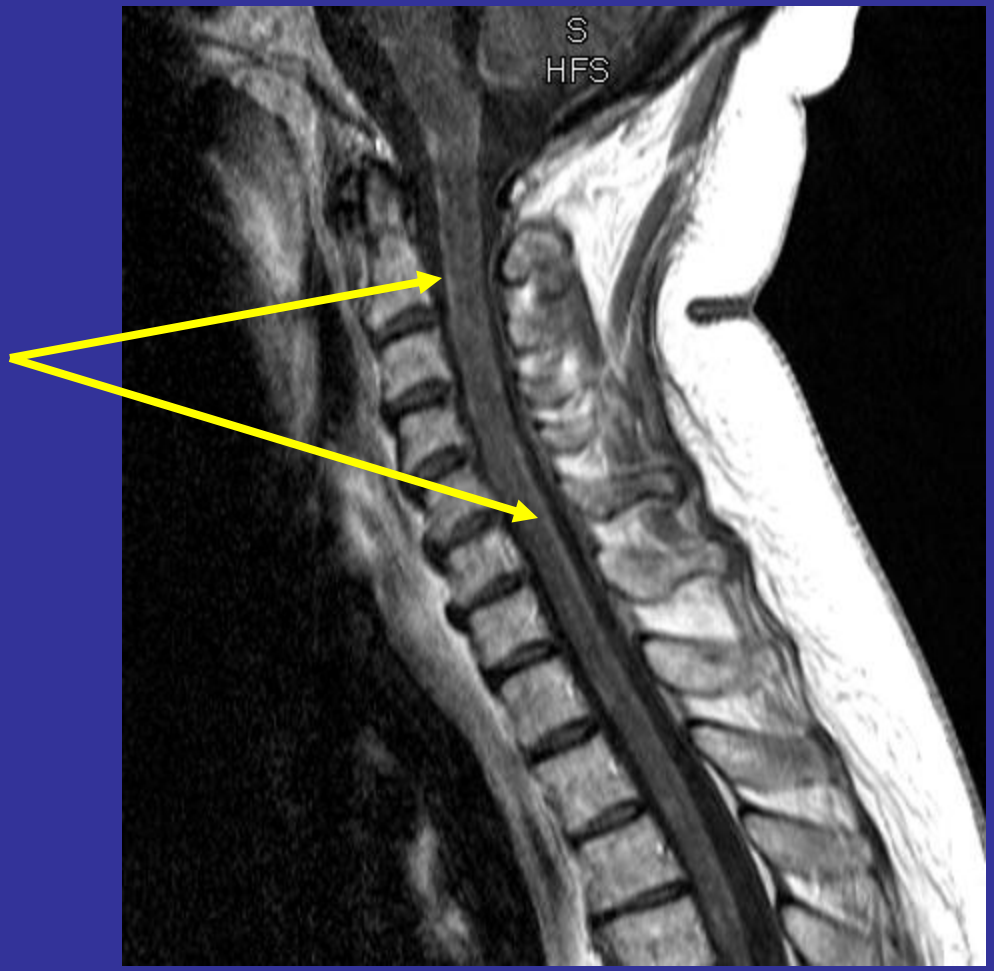








Courtesy of Dr. J. Corbett


S
HFS

Neuromuscular Investigations

- EMG / NCV
- Peripheral nerve biopsy
- Muscle biopsy
  - Symptomatic and asymptomatic (diagnostic) scenarios
  - ? MRI guided

Small Fiber Neuropathy

- Altered pain and temperature perception
  - Breastplate sensory changes
- Painful limbs and torso
- Autonomic dysfunction
  - Rarely pandysautonomia
- Small fiber neuropathy questionnaire
  - Hoitsma et al.
- Quantitative testing
  - Temperature and pain threshold
  - Sudomotor axon reflex (QSART)
  - Autonomic testing
- Skin biopsy with quantification of sensory and sudomotor nerve axons

Therapeutic Decisions

- No rigorous studies to define optimal therapy
  - Case series and “expert” opinion
- Therapeutic decisions should be guided by:
  - The patient’s clinical course
  - The expected “natural” history of the patient’s clinical manifestations
  - Adverse treatment effects

“Natural History” Clinical Course

- Monophasic illness: 2/3 of patients
  - Isolated cranial neuropathy, typically involving the facial nerve
  - Aseptic meningitis
- Progressive or remitting-relapsing illness: 1/3 of patients
  - CNS disease: parenchymal abnormalities, hydrocephalus, multiple cranial neuropathies (II and VIII)
  - Peripheral neuropathy
  - Myopathy

Monophasic Illness

- Prednisone 0.5 – 1.0 mg / kg / day (40 – 60 mg / day)
  - One or two weeks of full dose therapy
  - Taper over the next few weeks
- More prolonged therapy may be necessary depending on the clinical course

CNS Parenchymal and Severe Neuromuscular Disease

- Prednisone 1.0 mg / kg / day
  - Observe on this dose for 2 – 4 weeks
- Taper slowly
  - 5 mg every 2 weeks
  - Anticipate exacerbation at 10 mg / day (0.1 mg / kg / day)
    - Re-evaluate for disease activity: MRI, etc.
    - Patients often have their own “baseline dosage” below which exacerbations occur
  - Taper by 1 mg every 2 – 4 weeks at doses below 10 mg / day
- If clinical relapse, double dose (or 10 – 20 mg / day)

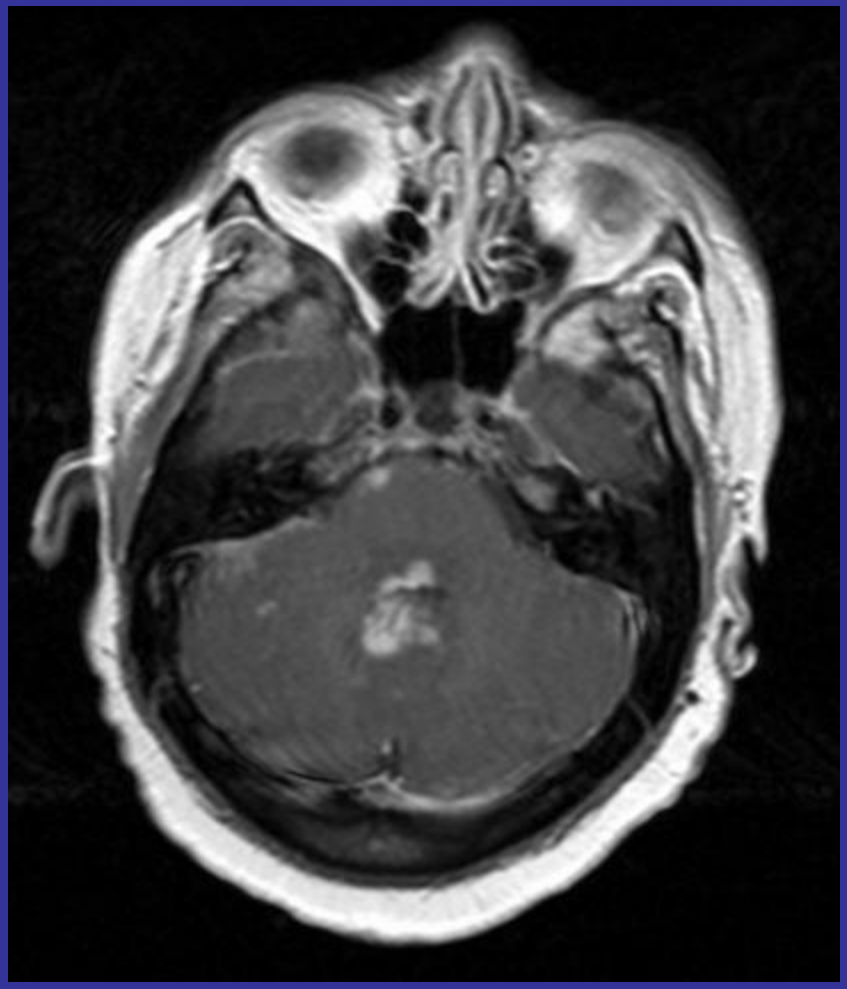
Parenchymal Disease

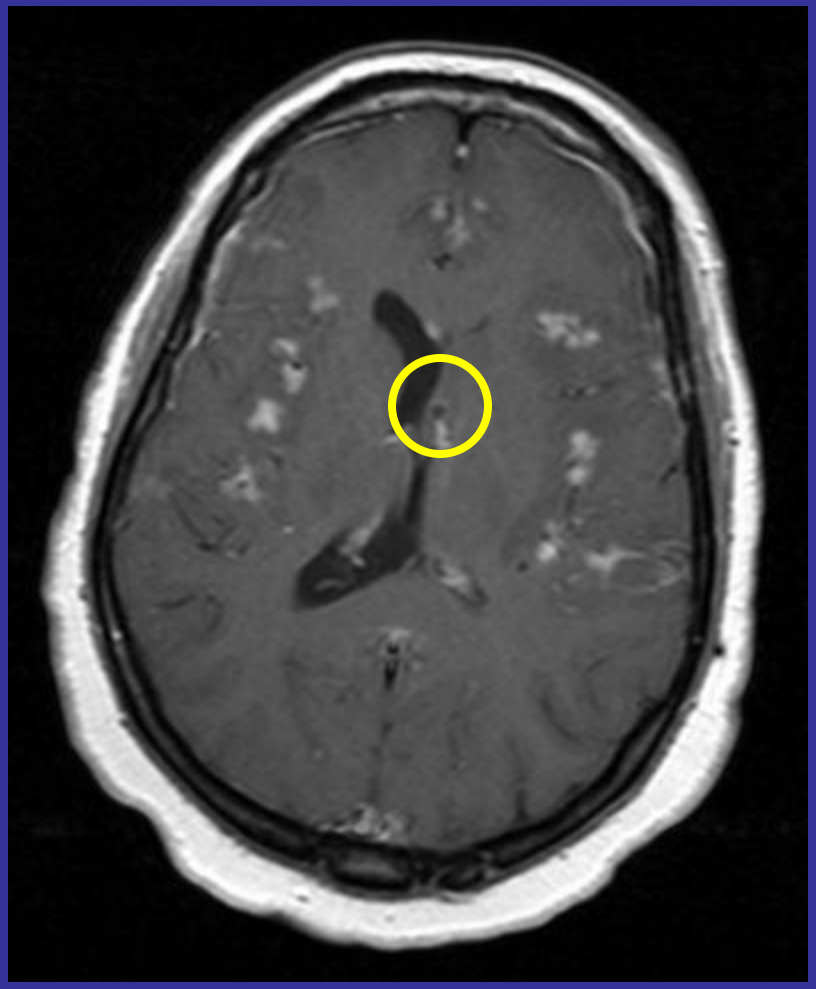
- Rarely does immunosuppressive therapy improve neuroendocrine function or vegetative symptoms
- Seizure control linked to control of underlying inflammatory disease

Krumholz, et al. 1991

Ventricular Enlargement

- Asymptomatic enlargement
  - Observe
- Mild, symptomatic hydrocephalus
  - Corticosteroid therapy
- Life-threatening or corticosteroid-resistant hydrocephalus
  - Ventricular shunting
  - Corticosteroid therapy + adjuvant modalities
- Rapid neurologic deterioration can occur
  - Especially following a LP





Shunt

Shunt Risk

- Shunt obstruction from inflammation
  - “Trapped ventricles”
- Infection
- Educate patients and caregivers when to seek emergent care
  - Copy of CT or MRI showing ventricular size

Acute, Severe Disease

- Methylprednisolone 20 mg / kg / day x 3 days
  - Followed by prednisone 1.0 mg / kg / day
- Infliximab infusions
  - In addition to other immunosuppressive strategies

Alternate or Adjunct Therapies

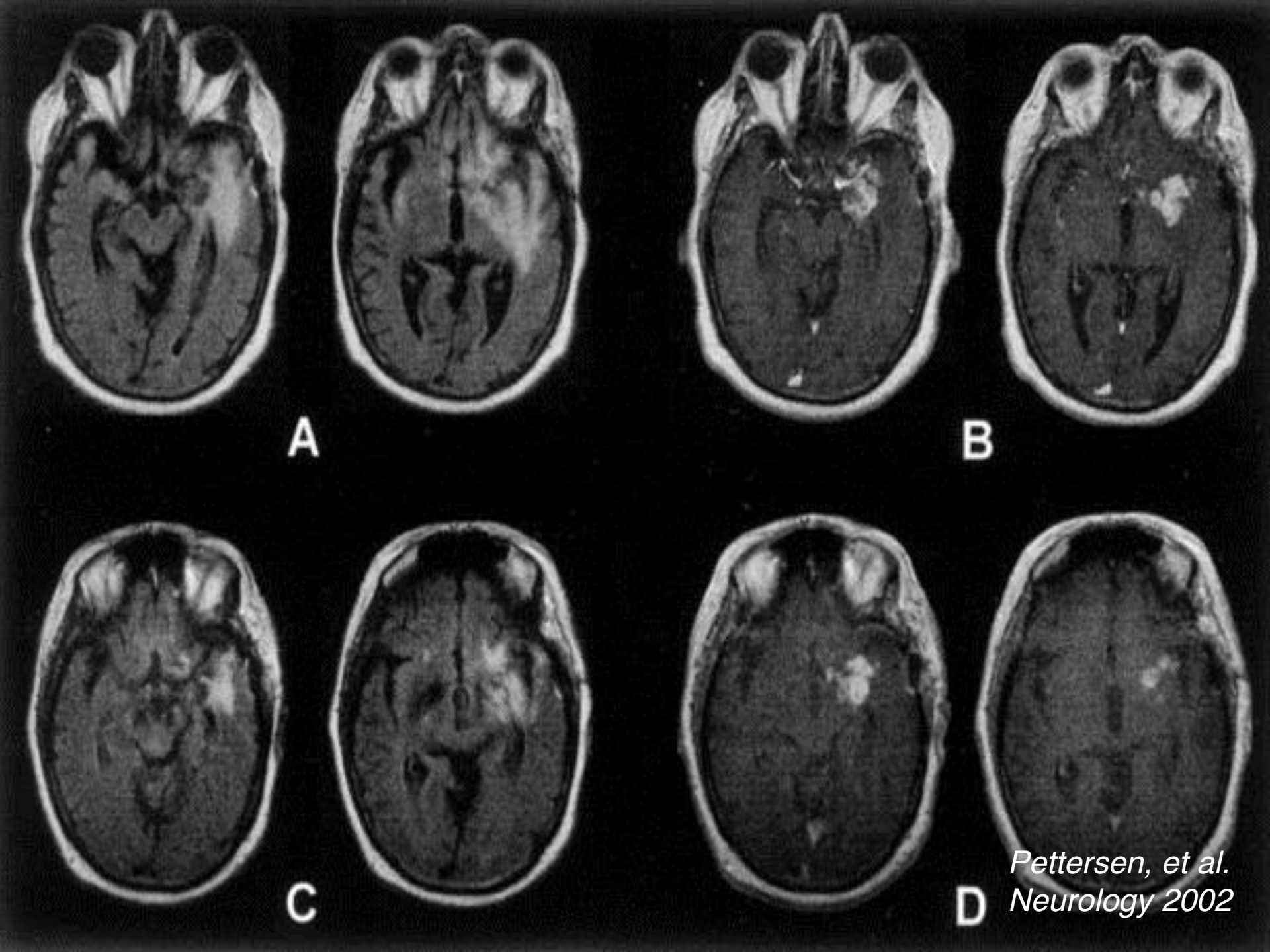
- Limited experience: case reports and series
- Indications
  - Need to avoid corticosteroids as initial therapy
  - Serious adverse corticosteroid effects
  - Disease activity in spite of aggressive corticosteroid therapy
- Rarely able to withdraw corticosteroid therapy completely but often able to decrease corticosteroid dose
- Trend to early use of these therapies for high risk patients

Alternate or Adjunct Therapies

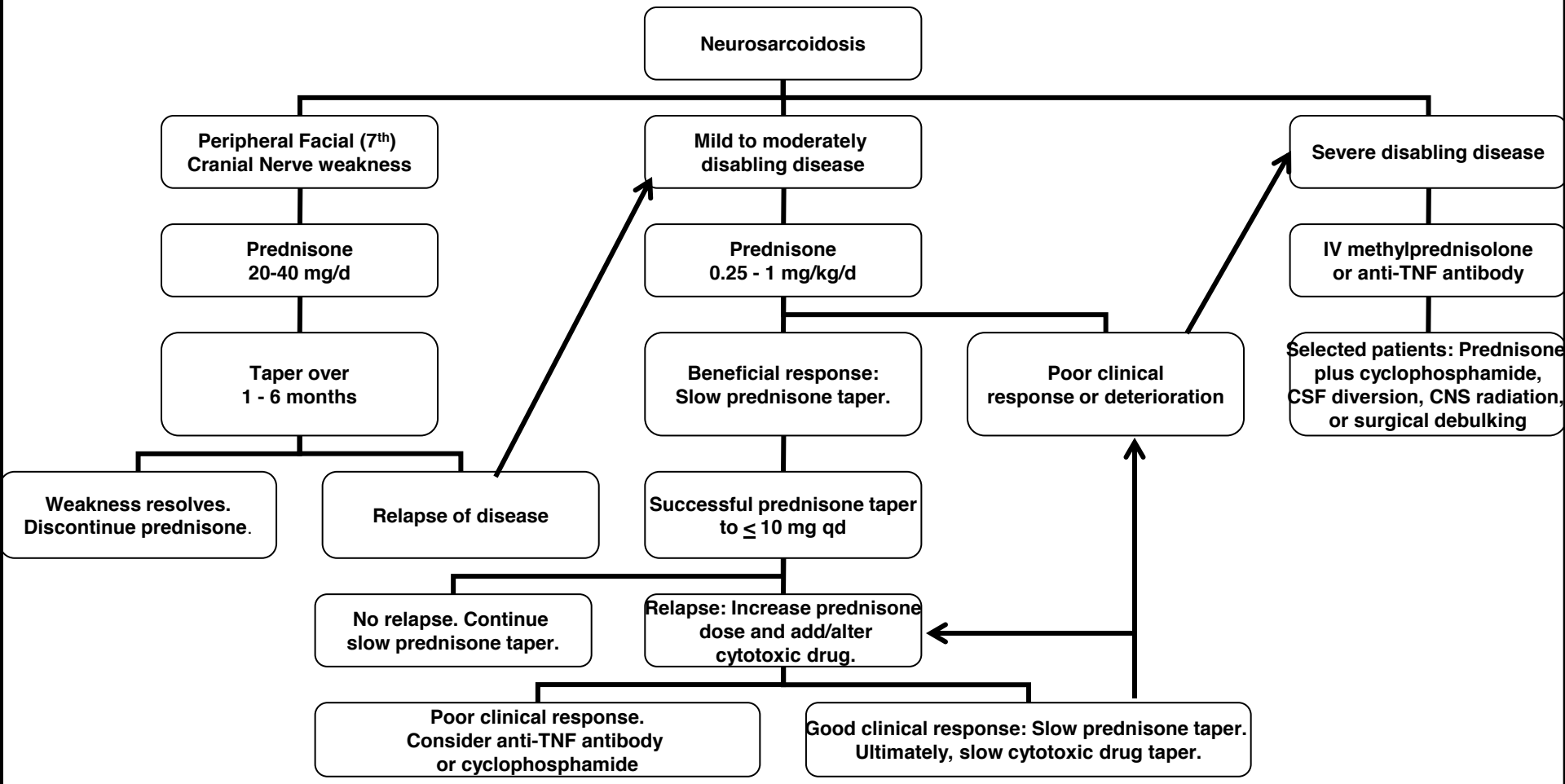
- Immunosuppressive medications
  - Azathioprine
  - Methotrexate
  - Mycophenolate mofetil
  - Cyclophosphamide
  - Cyclosporine
  - Chlorambucil
  - Cladribine
- Avoid drugs that have adverse effects on an already compromised organ

Alternate or Adjunct Therapies

- Immunomodulatory medications
  - Hydroxychloroquine
  - Thalidomide
  - Pentoxyfillin
  - Monoclonal antibodies to TNF-α
    - Infliximab
    - Adalimumab
    - Etanercept
  - Minocycline
  - IVIg for small fiber neuropathy
- Radiation therapy for CNS disease



Pettersen, et al.
Neurology 2002


Neurosarcoidosis
Peripheral Facial (7th) Cranial Nerve weakness
Mild to moderately disabling disease
Severe disabling disease
Prednisone 20-40 mg/d
Prednisone 0.25 - 1 mg/kg/d
IV methylprednisolone or anti-TNF antibody
Taper over 1 - 6 months
Beneficial response: Slow prednisone taper.
Poor clinical response or deterioration
Selected patients: Prednisone plus cyclophosphamide, CSF diversion, CNS radiation, or surgical debulking
Weakness resolves. Discontinue prednisone.
Relapse of disease
Successful prednisone taper to ≤ 10 mg qd
No relapse. Continue slow prednisone taper.
Relapse: Increase prednisone dose and add/alter cytotoxic drug.
Poor clinical response. Consider anti-TNF antibody or cyclophosphamide
Good clinical response: Slow prednisone taper. Ultimately, slow cytotoxic drug taper.

General Care Measures

- Exercise training
- Dietary programs
- Rehabilitation
- Treatment of depression
- Hormone replacement
  - Hypothyroidism and hypogonadism
- Supplemental “stress” corticosteroids
- Osteoporosis screening and treatment
- Fatigue
  - Possibly related to high circulating cytokine levels
  - Exercise intolerance (pulmonary, cardiac, or deconditioning), depression, obesity, hypothyroidism, hypogonadism, corticosteroid myopathy, occult neuromuscular disease, painful small fiber neuropathy
  - Sleep disorder – sleep apnea, primary hypersomnia
  - Modafinil, ? TNF-α antagonists

Long Term Complications

- Cryptococcal and tuberculous meningitis
- Toxoplasmosis
- Progressive multifocal leukoencephalopathy
- *Listeria monocytogenes* infection
- Spinal epidural lipomatosis
- Corticosteroid-induced myopathy
- Lymphoma
- Inclusion body myositis

If a patient is not doing well, the diagnosis of sarcoidosis should be questioned, alternate causes investigated, and a search for intercurrent complications begun.

Do not simply attribute the patient's deterioration to "active sarcoidosis" and reflexively increase the intensity of immunosuppression.