

NEUROSARCOIDOSIS, PACHYMENINGITIS, BEHCET'S DISEASE

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LECTURE GOALS

- 1) To provide an update on neurosarcoidosis and neurological symptoms common in patients with systemic sarcoidosis
- 2) To provide an update on the differential diagnosis and treatment of pachymeningitis, which is frequently autoimmune in origin
- 3) To provide an update about neuro-Bechet's and neurological symptoms common in patients with Behcet's Disease

Neurosarcoidosis

Sarcoidosis is defined as a multisystem, inflammatory disorder characterized by non-necrotizing granulomatous inflammation. The most common organ systems affected in sarcoidosis include the lungs, deep lymph nodes, skin and eyes, though neurological and cardiac organ system involvement, while rarer, accounts for substantial morbidity and mortality of the disease.¹⁻³

Neurological organ system involvement in sarcoidosis occurs in about 5-15% percent of sarcoidosis cases. Isolated neurological organ system involvement, most typically isolated CNS involvement, can occur in up to 1/3 of CNS sarcoidosis cases – it is not yet clear if the biology/risk factors are different in isolated CNS disease vs multi-organ-system disease, but given that the neuropathology and response to treatment appears to converge both phenotypes are currently considered to fall under the neurosarcoidosis umbrella (which is not the case for some other organ systems in which isolated non-infectious non-caseating granulomatous inflammation can occur and which is considered separate from sarcoidosis).

Genetics and Named Sarcoidosis Phenotypes

Sarcoidosis is a complex genetic disorder with numerous HLA associations similar to the kinds of genetic risk patterns seen in other autoimmune diseases. Genetics appears to influence risk of sarcoidosis, but not necessarily risk of organ system involvement (i.e. there are reports of one monozygotic twin with pulmonary sarcoidosis and the other with neurosarcoidosis). Heterogeneity in defining “neurological” sarcoidosis could influence study of risk factors in this context, and more rigorous case definitions of neurosarcoidosis have the potential to improve study in this area going forward.

There are several eponymous syndromes associated with sarcoidosis that may also have a genetic influence on risk, including:

- Lofgren Syndrome (Hilar lymphadenopathy, erythema nodosum, arthritis; Scandanavian ancestry predominance; benign prognosis at 2 years)
- Heerford Syndrome (a.k.a. Uveo-parotid Fever, with Uveitis, Fevers, Parotitis, can have facial palsy secondary to parotid swelling)
- Blau Syndrome (a.k.a. very early onset sarcoidosis with granulomatous arthritis, uveitis, dermatitis, associated with mutations in NOD2 that are not seen in adult sarcoidosis).

Epidemiology of Sarcoidosis and Neurosarcoidosis

The epidemiology of sarcoidosis varies by geography and is thought to be able to occur in potentially all populations globally. In the Nurses Health Study II, the average annual incidence rate was 11/100,000 and baseline prevalence was 100/100,000.⁴ In African-Americans, the prevalence of sarcoidosis is 35-71 per 100,000,

and there is a 3x more common age-adjusted incidence of sarcoidosis in African Americans (and in blacks in South Africa).⁵ Risk is also relatively higher in Scandinavia compared to other parts of Europe. In the 1999 NIH-funded ACCESS case-control study of sarcoidosis in the US, no clear causative environmental factors could be identified. There have been several studies reporting possible associations between various infections and sarcoidosis, most compellingly with mycobacteria, as patients with sarcoidosis can exhibit antigenic responses to mycobacterial antigens and gene expression profiling of whole blood has some similarities to patterns seen in active TB though also many differences, further work in this area is ongoing. By current pathological definitions, evidence of active mycobacterial infection would be considered just that and not neurosarcoidosis or sarcoidosis. Using metagenomic next-generation sequencing approaches for pathogen detection at UCSF, we have not identified evidence of active CNS infection in any of our pathologically-proven neurosarcoidosis cases to date, though study is ongoing and there always remains risk of misdiagnosis even with seemingly confirmatory pathology.

Immunology of Sarcoidosis

The immunology of neurosarcoidosis is predominantly inferred from study of pulmonary sarcoidosis and much remains to be learned for CNS and PNS specific manifestations. The emerging model in pulmonary sarcoidosis is that sarcoidosis is probably a TH17 (and not just TH1) process. CD4 T cells isolated from people with sarcoidosis are partially oligoclonal and antigen specific.

Neuropathology of Sarcoidosis

The pathological hallmark of neurosarcoidosis is the non-caseating (non-necrotizing) granuloma, which tends to be well-formed and compact. Rare necrosis may be seen on neuropathology in true neurosarcoidosis, especially if the biopsy is large, but any necrosis should be a red flag for possible infection and alternate diagnoses. Granulomas are organized collections of monocytes/macrophages, including with multinucleated fused monocytes called giant cells, along with associated B and T cells. There also tends to be a perivascular prominence to granulomatous inflammation in the CNS. Even with an otherwise textbook biopsy, the pathologist can only sign out that the findings are consistent with sarcoidosis but clinical correlation and strong phenotyping will always be needed to exclude infection and mimics as there can be sampling error (where necrotizing features/infection are not sampled) or sarcoidosis like reactions (such as to lymphoma).

Diagnosis of neurosarcoidosis

Diagnosis of neurosarcoidosis is based on level of certainty – definite, probable, possible. Sarcoidosis is fundamentally a pathology-driven diagnosis, and care should be taken to reserve the sarcoidosis label for this specific granulomatous autoimmune syndrome and not as a more general term for any atypical CNS inflammatory condition. There are several different criteria in the literature, more similar than different, and efforts are ongoing to standardize and modernize.

- **Definite neurosarcoidosis** requires pathological confirmation of granulomatous
- **Probable neurosarcoidosis** requires a neurological syndrome consistent with active granulomatous inflammation and biopsy evidence of sarcoidosis in another organ system following rigorous exclusion of other causes
- **Possible neurosarcoidosis** is defined by a consistent neurological syndrome consistent with active granulomatous inflammation from sarcoidosis but no biopsy confirmation and no known sarcoidosis in another organ system
- **Small fiber neuropathy in sarcoidosis**⁶ is best considered a para-neurosarcoidosis manifestation, as are **other common neurological complaints in patients with systemic sarcoidosis, such as cognitive complaints and fatigue without evidence of active CNS inflammation**, which likely relate to sarcoidosis though could be multifactorial

In some circumstances (i.e. spinal cord or brainstem inflammation not amenable to biopsy) probable neurosarcoidosis is more than adequate, and in some circumstances (i.e. isolated spinal cord involvement) empiric treatment of possible neurosarcoidosis may be what is best for the patient even if such labeling might preclude inclusion in observational or interventional trials. But such labels can be very helpful in signaling level of uncertainty and need to reinvestigate the cause or consider more invasive diagnostics, especially when not responding to treatment.

A chest CT with contrast to look for pulmonary sarcoidosis is probably the most helpful first test when seriously considering neurosarcoidosis. Whole body FDG-PET can be very helpful in identifying metabolically active “hot” lymph nodes amenable to biopsy that may show up as normal on CT (because they are “hot” but not enlarged). The sensitivity of ACE in serum and CSF is very poor (<20% of biopsy confirmed neurosarcoidosis cases in the UCSF experience) and also suffers from poor specificity.

Key observations about CNS sarcoidosis

- The CNS syndrome is typically the presenting syndrome that leads to sarcoidosis diagnosis; diagnosis of prominent CNS sarcoidosis is less common in people who already have known sarcoidosis
- The clinical syndrome is secondary to the affected neuroanatomy (i.e. meningitis, myelitis, optic nerve involvement, hypophysitis, etc) and neurological localization is most helpful for diagnosis
- Once sarcoidosis seeds the CNS it tends to infiltrate and spread locally and also has a propensity for the meninges. Relapses in novel sites (i.e. a new optic neuritis in someone that has only ever had myelitis) are much less typical than would be the case in diseases like MS or NMO and should raise concern for alternate causes (i.e. infection)
- The disease can wax and wane for years, including with persistent enhancement on MRI following the administration of gadolinium for months to years at a time (very few processes do this in clinical neurology, especially when the MRI often looks worse than the general appearance and neurological examination of the patient might suggest)

Key observations about PNS Sarcoidosis

- The neuropathy phenotype can be heterogenous, including polyneuropathy, multiple mononeuropathies, radiculopathy/plexopathy. Biopsy is often needed to confirm active granulomatous inflammation vs other causes of neuropathy, even in patients with proven systemic sarcoidosis. It is important to evaluate for other risk factors, including toxicities of treatment and comorbidities that can cause neuropathy.
- Concomitant muscle biopsy at the time of nerve may be very helpful (positive in up to 80% of patients) and also help diagnostically in some circumstances (i.e. leprosy would just affect nerve, not muscle).

Treatment of Neurosarcoidosis

While there are several randomized controlled trials of treatments for pulmonary sarcoidosis, treatment of neurosarcoidosis is currently informed by case series, expert opinion and inferring from pulmonary sarcoidosis trial data.

In general, glucocorticoids are the mainstay and first-line treatment for neurosarcoidosis, often said to be sufficient in about 50% of cases, though the doses needed to control the disease can be toxic and prohibitive. Typical first-line steroid-sparing options include methotrexate, azathioprine and infliximab (a TNF-alpha inhibitor). While mycophenolate mofetil is often used in the neurosarcoidosis context, there is very little data (i.e. no trials) in pulmonary sarcoidosis unlike the case for methotrexate, azathioprine and infliximab, and observational data suggests higher rates of relapse, though it may be more tolerable for some patients. There is emerging data for the benefit of infliximab even in otherwise treatment-refractory cases. There are reports about treatment with Rituximab for pulmonary and neurosarcoidosis but more study and experience is needed. There may also be a role for hydroxychloroquine and leflunomide in some contexts, and cyclophosphamide in others.

Pachymeningitis

Pachymeningitis – inflammation of the pachymeninges (dura)
(as opposed to leptomeningitis, inflammation of the leptomeninges (pia and arachnoid))

Pachymeningitis can be a vexing diagnostic and treatment challenge for neurologists and rheumatologists. Diagnosis can be challenging given that

- 1) the CSF examination samples the subarachnoid space in which CSF circulates and does not directly sample the pachymeningeal space reducing diagnostic sensitivity

- 2) biopsy is often needed to secure a firm diagnosis but even when confirming pachymeningitis may not point towards a more specific etiology
- 3) disease associations may overlap with risk for infection and autoimmunity and malignancy (i.e. a patient with rheumatoid arthritis on immunosuppression with pachymeningeal inflammation is at risk for RA associated autoimmune pachymeningitis, CNS infection from immunosuppression, malignancy risk from immunosuppression)

Diagnosis of pachymeningitis typically starts with the finding of dural enhancement on brain MRI. It is important to consider the radiological differential for dural enhancement, which includes

- Syndrome of Intracranial Hypotension (SIH), i.e. low CSF pressure (most typically with uniformly symmetric dural enhancement and other signs of “sagging brain”)
- Malignant: Meningioma, metastasis
- Vascular: Thrombosis; Hematoma; Dural AVF/venous tortuosity; secondary venous engorgement

The differential of pachymeningitis is broad.⁷ Major considerations include:

CNS Infection: especially TB^{8,9} but also bacterial, fungal, other mycobacterial, parasitic, much less typical of viral

Autoimmune/Rheumatologic: Idiopathic hypertrophic pachymeningitis;¹⁰ IgG4 related disease (accounts for a subset of previously “idiopathic” pachymeningitis in some series when went back to restudy the pathology once this syndrome was defined);¹¹⁻¹³ ANCA/Granulomatosis with polyangiitis associated;¹⁴ rheumatoid arthritis or other connective tissue disease associated, neurosarcoidosis (see above)

The neuropathology can be very helpful in clarifying the above, if there are granulomas, evidence of vasculitis, IgG4 staining and associated findings, etc.

Treatment is currently empiric. Glucocorticoids are the mainstay but responses often incomplete and toxicity high. There may be a role for steroid-sparing agents like methotrexate, azathioprine, mycophenolate mofetil and cyclophosphamide in some cases. There is emerging data for the use of B-cell depleting (anti-CD20) therapies for IgG4 related disease, ANCA associated pachymeningitis and idiopathic cases. Infliximab can be helpful for neurosarcoidosis (see above). TB therapy (RIPE) may be needed first in select cases in which there is concern for TB (i.e. +PPD/quantiferon without an explanation, necrosis on neuropathology, epidemiological risk factors).

Neuro-Behcet's

Behcet's disease is an inflammatory disorder characterized phenotypically by recurrent oral aphthous ulcers, genital ulcers, uveitis and skin lesions (pustular/acneiform type lesions or erythema nodosum-like). There may also be arthritis, bowel inflammation and central nervous system involvement or associations.¹⁵ There is a propensity for “pathergy” (development of a large papule following a needleprick to the skin) in some patients, but not all. Behcet's appears to be an autoimmune disease with a propensity for certain HLA haplotypes and increased risk with ancestry tracing back to the Silk Road (especially Turkey, Syria, through to Central and East Asia). The pathology can show a leukocytoclastic vasculitis but may have more nonspecific inflammation. Published neuropathology is more limited and somewhat nonspecific but can include perivascular cuffing of T cells and monocytes with neuronal apoptosis.¹⁶ There are several proposed diagnostic criteria, including the 1990 International Study Group criteria.¹⁷

There are also 2016 consensus recommendations for neurological involvement in Behcet's Disease.¹⁸ The International Study Group requires:

- Recurrent oral ulceration that recurs at least 3 times in one 12 month period. These can be minor aphthous, major aphthous or herpetiform.

Plus 2 or more of the following:

- Recurrent genital ulcers (aphthous or scarring)
- Uveitis or retinal vasculitis
- Skin lesions (Erythema nodosum, pseudofolliculitis, papulopustular, acneiform)
- Positive pathergy test at 24-48 hours

Consensus recommendations for Neuro-Behcet's favor syndromic diagnosis and reserving neuropathology for mass lesions or diagnostic clarity.¹⁸

CNS involvement in Behcet's is divided into:¹⁸

- **Parenchymal involvement**, most typically inflammatory lesions involving the brainstem, brain or spinal cord, which can be mass lesions but are often multifocal. These can relapse and remit. CSF is often inflammatory. CSF IL-6 may be a marker of disease activity.
- **Non-parenchymal (i.e. vascular or meningeal) involvement**, including venous sinus thrombosis, arteritis, aneurysm. There can also be self-limited aseptic meningitis. Non-parenchymal involvement is often monophasic.
- Associations with PNS pathologies have been observed in patients with Behcet's but the pathophysiology/causation is less clear.
- Other neurological symptoms such as cognitive/neuropsychiatric complaints and migraine are said to be more common or at very least can be important comorbidities in people with Behcet's Disease.

Treatment for parenchymal/inflammatory lesions typically includes glucocorticoids. Steroid-sparing options include azathioprine (often preferred in the Behcet's community but no randomized data one way or another), methotrexate, MMF, cyclophosphamide. There is also emerging data for TNF-alpha inhibitors like infliximab. Steroids are also typically offered for venous sinus thrombosis in Behcet's; the role for anticoagulation is debated.

As with any syndrome in which there is no test, including biopsy, that can secure a final diagnosis, rigorous evaluation for other potential causes and mimics is essential to ensure accurate diagnosis.

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