Neuropsychiatric Syndromes: Neuroinflammation

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Disclosures

• No Financial Disclosures

• There will be discussion of pharmaceutical products being used for non-FDA approved indications
Goals

- Identify symptoms and signs of a neuroinflammatory syndrome
- Describe a relationship between inflammation and behavioral symptoms
- Explore diagnostic and treatment strategies in neuroinflammation
Systemic Inflammation and behavior

• 45% of non-depressed hepatitis C and cancer patients treated with INF-α develop depressive symptoms associated with increase serum IL-6 levels

• Patients with medical conditions associated with chronically elevated inflammatory markers have higher rates for mood disorders:
  • Obesity
  • Diabetes
  • Malignancy
  • Rheumatoid arthritis
  • Multiple sclerosis
  • Lupus

Dantzer et al., Nature Reviews Neuroscience 2008
Haroon et al., Neuropsychopharmacology 2012
Lupus, behavior, and inflammation

• Patients with Lupus, a systemic autoimmune disease, exhibit higher rates of:
  • Anxiety
  • Mood symptoms
  • Psychosis

• Hypothesis:
  the blood-brain barrier has broken down, allowing auto-antibodies enter the brain somehow leading to symptoms.

• 90% of Lupus patients with psychosis have auto-antibodies in CSF

Postal et al., CNS Drugs 2011
Para-neoplastic neurological syndromes

• Associated with systemic cancer.

• Due to auto-antibodies that affect the nervous system

• May affect any part of the nervous system:
  • Subacute sensory neuropathy
  • Chronic sensorimotor neuropathy
  • Acute sensorimotor neuropathy
  • Paraneoplastic autonomic neuropathy
  • Lambert-Eaton myasthenic syndrome
  • Dermatomyositis
  • Paraneoplastic neuromyotonia
  • Paraneoplastic encephalomyelitis
  • Limbic encephalitis

Dalmu et al, Brain Pathology 1999
Classical Neuroinflammation: Acute Limbic Encephalitis

- Depressed mental status
- Acute onset temporal lobe seizures, then refractory seizures
- Mood symptoms
- Psychotic symptoms
- Longstanding cognitive deficits

Proposed pathophysiology:
Auto-antibodies directed against neuronal proteins cross the blood-brain barrier, damaging the brain
Acute Limbic Encephalitis

• Usually associated with:
  • Small Cell Lung Cancer
  • Seminoma and other testicular tumors
  • Thymoma
  • Breast Cancer
  • Hodgkin Lymphoma
Anti-neuronal auto-antibodies cause Limbic Encephalitis:

- anti-NMDA receptor
- anti-Hu
- anti-Ma2
- anti-CRMP5
- LGI1 antibodies
- anti-AMPAR receptor
- anti-GABA-A receptor
- anti-GABA-B receptor
- anti-CASPR-2
- anti-IgLON5

Najjar et al., Journal of Neuroinflammation 2013
Autoimmune Limbic Encephalitis is not always para-neoplastic.

• No cancer is found in up to 15% percent of patients with para-neoplastic antibody associated autoimmune encephalitis.

• Some anti-neuronal auto-antibodies known to cause encephalitis are not associated with cancer:
  • anti-GAD (glutamic acid decarboxylase)
  • anti-VGKC (voltage-gated potassium channel)

Sillevis et al, J Neurology 2002
Autoimmune encephalitis is not always acute

• The inflammatory response associated with some auto-antibodies is milder than other auto-antibodies, resulting in a less severe presentation and milder symptoms overall.

• This leads to presentation of symptoms over months (indolent) rather than days to week (acute to subacute).

Gultekin et al, Brain 2000
Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis

- Presentation typically starts with headache, fever, and flu-like symptoms.
- Prominent psychiatric manifestations can include anxiety, agitation, bizarre behavior, hallucinations, delusions, and global disorganization.
- Insomnia
- Cognitive decline
- Seizures
- Decreased arousal
- Catatonia and echolalia
- Dyskinesias
- Autonomic instability with hyperthermia, fluctuating blood pressure and heart rate

Dalmau et al, Ann Neurol. 2007
Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis

• Varies in severity

• Can be associated with Ovarian Teratoma

• Diagnosis and treatment are often delayed when symptoms are milder.

• A study of the serum or CSF of 20 patients with “idiopathic encephalitis with dyskinesias” showed that 50% had anti-NMDA encephalitis.

• Another study of patients with dyskinetic “encephalitis lethargica” showed 20 of 20 patients had anti-NMDA encephalitis.

Dale et al, Ann Neurol 2009
Objective findings in NMDA Encephalitis

- Diagnosis is confirmed by detection of IgG antibodies to the NR1 subunit of NMDAR in serum or CSF.

- CSF: can be normal or show lymphocytic pleiocytosis and oligoclonal bands

- EEG: can be normal, or show generalized slowing and/or interictial epileptiform discharges.

- Brain MRI: normal or transient FLAIR or contrast enhancing abnormalities in the cortex or subcortex.
Objective findings in NMDA Encephalitis?

- There are NO consistent findings in NMDA Encephalitis other than the IgG antibodies to the NR1 subunit of NMDAR in serum or CSF.

- Generally, a characteristic clinical picture plus various suggestive immune markers and suggestive MRI, functional imaging, and EEG findings leads to CSF analysis searching for auto-antibodies known to cause encephalitis, including NMDA antibodies.

- Most cases that warrant treatment have +CSF antibodies for one the encephalitic syndromes.
Treatment of NMDA Encephalitis: Dalmau et al

- IVIG 0.4g/kg daily for five days and methylprednisolone 1 g/day for five days.

- If not significantly improved after 10 days, start second line therapy: rituximab 375 mg/m² combined with cyclophosphamide 750 mg/m². Follow with monthly cycles of cyclophosphamide.

- Treatment is continued until “substantial recovery occurs, which can take up to 18 months.

- Series of 577 patients, 81% had a good outcome. Relapse occurs in 15-24%, so immunotherapies are often continued for at least one year.

Dalmau et al, Lancet Nerorl. 2011
Titulaer et al, Lancet Neurol. 2013
Are there cases of Encephalitis without CSF Auto-antibodies?
Case One
Neuropsychiatric Autoimmune Encephalitis without VGKC-Complex, NMDAR, and GAD Auto-antibodies

21 year-old woman with onset of psychosis at age 15

- Psychosis worsened during menstruation with prominent negative psychotic symptoms:
  - social withdrawal
  - apathy
  - affective blunting
  - impoverished speech

- Inpatient psychiatric hospitalization for 4 weeks, followed by long term day-treatment program over six years.

Najjar et al., Cognitive and Behavioral Neurology 2013
Initial Workup and first six years of treatment

• At age 16 after onset of symptoms:
  • brain MRI was normal
  • Neuropsychological testing results revealed cognitive deficits beyond expectations:
    • FS-IQ 77 (6th percentile)
    • V-IQ of 93 (32nd percentile)
    • P-IQ of 55 (<1st percentile)
    • Prominent difficulties with language processing, memory, attention, mental flexibility, and decision making

• Over six years, treatment included:
  • Antipsychotics: olanzapine, risperidone, and quetiapine
  • Antidepressants: citalopram, escitalopram, paroxetine, fluoxetine, sertraline, venlafaxine, and buproprion
  • Benzodiazepines: clonazepam and lorazepam
Subsequent workup

• Complete blood counts, Complete Metabolic Profile, and Liver function tests were within normal limits

• Serum levels of ammonia, pyruvate, lactate, and ceruloplasmin were within normal limits

• Serum inflammatory markers within normal limits for:
  • ANA
  • anti-dsDNA antibodies
  • Sjogren antibodies
  • ANCA antibodies
  • Thyroglobulin antibodies
  • Thyroid peroxidase antibodies
  • Antigliadin antibodies
  • Antiphospholipid antibodies
  • C3, C4, CH50, and B2-glycoprotein
Workup, continued

• Endocrinological serum studies were within normal limits:
  • FSH, LH, prolactin
  • TSH, T3, T4
  • DHEA
  • β-HCG
  • Testosterone

• CSF analysis:
  • no wbc cells
  • normal glucose
  • normal protein concentration
  • no oligoclonal bands
  • No anti-NMDA, VGKC-complex, GAD, NMDAR, anti-Hu, anti-Ma2 or anti-CV2/CRMP5 antibodies.
More workup

- Serum and CSF pathogen analysis negative for:
  - Cryptococcus neoformans
  - Borrelia burgdorferi
  - Syphilis
  - Rickettsia
  - HSV-1 or HSV-2
  - HHV-6
  - CMV
  - VZV
  - Coxsackie
  - ECHO
  - Epstein-Barr
  - HIV-1 and HIV-2
  - Tropheryma whipplei
And still more workup

- Studies for inborn errors of metabolism were within normal limits

- Skin and bone marrow biopsies excluded such lysosomal storage diseases as Niemann-Pick type C and GM2 gangliosidosis

- Muscle biopsy was negative for mitochondrial disorders

- Chromosomal studies were normal

- Abdominal and pelvic CT did reveal occult malignancy

- Video-electroencephalogram showed diffuse slowing and no epileptiform activity
Treatment?

• Despite no laboratory evidence of inflammation, she was treated with a pulse of methylprednisolone and IVIG.

• Within a few weeks of this treatment, negative psychotic symptoms improved.

• Ten months later, negative psychotic symptoms recurred and imaging was repeated.
Follow up imaging

- At age 23, seven years after presentation Brain MRI showed widespread bi-hemispheric cortical and sub-cortical non-enhancing lesions:
Brain Biopsy?

Mild perivascular mixed inflammatory infiltrate

Mild to moderate microglia activation
Revised Treatment

• Because of the biopsy evidence for neuroinflammation, she was treated with plasma exchanges:
  • 20 daily exchanges, 4 cycles
  • After every 5 exchanges, she took a 4-day tapering course of oral steroids

• No improvement in negative psychotic symptoms

• No improvement in functioning
Repeat Imaging

• Significant improvement in imaging, 8 years from initial presentation:
Seronegative Autoimmune Encephalitis

• Why aren’t antibodies found in the serum?
  • Serum is negative for antibodies because the symptoms are not due to antibodies
  • Auto-antibodies are novel and have not yet been identified
  • Auto-antibody levels declined as the illness moves to a chronic phase
The bottom line

• This patient has what we would consider schizophrenia with negative symptoms

• She received treatment as usual for years without improvement

• There was transient improvement with immunotherapies

• Brain biopsy showed inflammation in areas of the brain that were abnormal on MRI

• There were no CSF antibodies, but pathologic evidence of encephalitis.

• Immune treatment did not make any difference for her.
Case Two
Brain Biopsy Findings Link Major Depressive Disorder to Neuroinflammation, Oxidative Stress, and Neurovascular Dysfunction: A Case Report

• 39 year-old man with onset of depressive mood symptoms at age 15

• Baseline dysthymia persisted throughout teens and twenties

• Academic performance and personal achievement remained stellar

• Age 29, first major depressive episode, prominent hypersomnia and anergia and he was psychiatrically hospitalized

Najjar, Pearlman, Hirsch, Friedman, Strange, Reidy, Khoukaz, Ferrell, Devinsky, Najjar, and Zagzag
Biological Psychiatry 2013
Course

• Treated with a combination of psychotherapy and psychoactive medications, which continued going forward

• Only a partial response

• By age 35, the patient could not sustain work because of persistent mood symptoms and cognitive difficulties

• Over the next four years:
  • Brain MRI was unremarkable
  • Neuropsychological testing was remarkable only for high FSIQ
  • EEG and sleep studies were unremarkable
Treatment

• Age 38, diagnosed with neurological complications of Lyme disease.

• Treated with antibiotics, acupuncture, over-the-counter supplements, transcranial magnetic stimulation, and hyperbaric oxygen

• Psychoactive medications were optimized:
  • fluoxetine
  • bupropion
  • quetiapine
  • clonazepam
  • dextroamphetamine

• No improvement noted
My evaluation

• At age 39, after 10 years of psychotherapy, he terminated treatment and sought neuropsychiatric evaluation

• Comprehensive neurological physical examination was unremarkable

• Appearance: Older than expected, limited hygiene and grooming; psychomotor slowing
• Affect: reactive; dysphoric, anxious, and irritable
• Mood “depressed and worried”
• Thought process: Slow, goal-directed
• Thought content: ruminative, hopelessness, wish for life and suffering to end, passive suicidal ideation
• Sensorium: Highly intelligent, abstract thinker. Excellent memory and attention.
Quantitative Measures

- MOCA score 30/30
- Montgomery-Asberg Depression Scale (MADRS) score 25
- Beck Depression Inventory (BDI-II) score 27
- Beck Anxiety Inventory (BAI) score 22
- Neuropsychological testing results revealed cognitive strengths beyond expectations given his complaints about cognition:
  - FS-IQ 127 (96th percentile)
  - V-IQ 141 (99.7th percentile)
  - P-IQ 119 (90th percentile)
  - Processing speed “average”
Workup

• Comprehensive serological and cerebrospinal fluid assays for infectious agents, systemic autoimmune diseases, and anti-neuronal antibodies were all unremarkable

• 72 hour ambulatory electroencephalogram was normal

• Brain MRI: scattered white matter foci of increased signal

• Single photon emission computed tomography (SPECT): moderate to severe frontal hypo-perfusion
Diagnosis and Treatment Plan

• Diagnosis: Major Depressive Disorder.

• Referred to NYU Langone Treatment Resistant Depression Program

• Dr. Norman Sussman:
  • added memantine, glutamatergic effects could improve cognitive and mood symptoms
  • recommended ECT

• Patient refused ECT due to concerns about cognitive effects

• No improvement
Brain biopsy?

• Given worsening symptoms, the abnormal but nonspecific brain MRI and SPECT imaging findings, and his concerns about ECT, I consulted Dr. Souhel Najjar about the possibility of seronegative autoimmune encephalitis

• The patient agreed to a brain biopsy to determine whether there was any evidence of neuroinflammation
Microscopy: activated microglia

CD68 x400
Microscopy: mild, focal, and perivascular histiocytic infiltration

CD63 x400
Microscopy: mild to moderate subcortical white matter astrogliosis

glial fibrillary acidic protein x400
Ultrastructural analysis: lipofuscin granule accumulation within the neurovascular unit

low magnification

high magnification

E: endothelial cell
P: pericyte
L: Lumen of capillary
Lipofuscin granule accumulation?

- Lipofuscin is the product of unsaturated fatty acid oxidation
- Symptomatic of membrane damage, damage to mitochondria, or damage to lysosomes
- Accumulation of lipofuscin suggests imbalance between formation and disposal mechanisms, seen in:
  - Neuronal ceroid lipofuscinosis, a neurodegenerative disorder
  - Amyotrophic lateral sclerosis
  - Alzheimer's disease
  - Parkinson's disease
- Unclear why it was found in this patient.
What do the brain biopsy results mean?

• The typical brain does not have evidence of:
  • activated microglia
  • perivascular histiocytic infiltration
  • astrogliosis
  • lipofuscin granule accumulation

• While the medical literature had previously documented increased central nervous system oxidative stress in MDD, this was the first demonstrated evidence of oxidative injury of the neurovascular endothelium.

• These findings taken together are evidence of inflammation and cellular-level dysfunction of the brain: **Encephalitis.**
What can we do about it?

**IVIG**

- Intravenous immunoglobulin (IVIG): used for a wide range of autoimmune and inflammatory diseases.
- Should cross into the brain if there is blood-brain barrier breakdown.
- Despite the broad efficacy of IVIG therapy, its modes of action remain unclear.
- **IVIG Paradox:** the same class of molecule that promotes pathology in a disease also used to treat the very same disease.
- Because IVIG is obtained from pooled sera of 1000’s of vaccinated adults with their own auto-antibodies, IVIG contains antibodies directed against cytokines and antibodies:

  Destroy “bad” auto-antibodies with “good” auto-antibodies

Schwab and Nimmerjahn, Nature Reviews Immunology 2013
What else can we do about it?

Minocycline

- Microglial activation and oxidative injury:
  - In vitro: minocycline inhibits microglial activation and proliferation, cytokine secretion, and nitric oxide synthetase (Henry et al., Journal of Neuroinflammation 2008)
  - Small randomized, double-blind placebo-controlled trial: minocycline improved schizophrenic negative symptoms and cognitive dysfunction (Leuvokitz et al., Journal of Clinical Psychiatry 2010)
The Treatment

• After confirming presence of inflammation in the brain, immunomodulatory treatment was started:
  • 0.5 g/kg IVIG pulse therapy twice weekly for nine months
  • Three months later, intravenous minocycline 100 mg twice daily for six months:
  • Psychotropic regimen remained constant
Result: 10 months after treatment, repeat SPECT scan showed normalization of frontal hypo-perfusion.
Clinical Result

• 13 months after treatment, the patient and family reported mood, anxiety, and cognitive symptoms improved significantly:
  • MADRS score decreased from 25 to 15
  • BDI-II score decreased from 27 to 15
  • BAI score decreased from 22 to 3

• 18 months after treatment, the patient and family reported the best-sustained improvement in mood symptoms since age 15:
  • MADRS score was 8.
  • Patient’s wife: “I can't tell you how much I appreciate your efforts and those of Dr. Najjar's over the past few years, and I hate to think where he'd be if we hadn't found you.”
For Your Consideration

• Do many idiopathic neuropsychiatric syndromes have an auto-immune etiology?

• Recent meta-analysis of 7 studies of patients with schizophrenia tested for NMDA showed:
  • 115 of 1441 patients, nearly 8% had serum NMDA antibodies

• How should these patients be further evaluated and treated?

Pollak et al, Psychological Medicine, 2013
Summation

• IVIG, Plasmapheresis, corticosteroids, and other immunosuppressive agents are used to treat autoimmune encephalitis

• In acute autoimmune encephalitis, the inflammation is intense. Imaging shows contrast enhancement, indicating blood-brain barrier breakdown

• There are indolent presentations of autoimmune encephalitis that can present as primary psychiatric disorders with chronic, mild inflammation.

• Treatment with our current immune therapies suppresses inflammation systemically, which can cause tremendous harm.

• Without CSF antibodies confirming a diagnosis, immunotherapy is not recommended at this time.